CRITICAL CARE

z.f



www.mansdocs.com
we reach all doctors
/ MansDocs

CRITICAL CARE

Chief Editors

Narendra Rungta MD FISCCM FCCM FICCM
President—Indian Society of Critical Care Medicine
Association of SAARC Critical Care Societies
Jeevan Rekha Critical Care and Trauma Hospital
Jaipur, Rajasthan, India

Rajesh Pande MD PDCC (SGPG IMS) FICCM FCCM (USA)
Director
Critical Care and Emergency Medicine
BLK Superspeciality Hospital
New Delhi, India

Editors

Manish Munjal MD FICCM
Vice President
Jeevan Rekha Critical Care and Trauma Hospital
Jaipur, Rajasthan, India

Sudhir Khunteta MD
Chief Internist and Critical Care Specialist
Shubh Hospital
Jaipur, Rajasthan, India

Foreword

Shirish Prayag MD FCCM



The Health Sciences Publisher
New Delhi | London | Panama | Philadelphia

by mansdocs.com

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters
Jaypee Brothers Medical Publishers (P) Ltd.
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
E-mail: jaypee@jaypeebrothers.com

Overseas Offices
J.P. Medical Ltd.
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-20 3170 8910
Fax: +44(0)20 3008 6180
E-mail: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
E-mail: cservice@jphmedical.com

Jaypee Medical Inc.
The Bourse
111 South Independence Mall East
Suite 835
Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
E-mail: jpmed.us@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
17/1-B, Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
E-mail: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
Bhotahity, Kathmandu, Nepal
Phone: +977-9741283608
E-mail: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

© 2016, Jaypee Brothers Medical Publishers

The views and opinions expressed in this book are solely those of the original contributor(s)/author(s) and do not necessarily represent those of editor(s) of the book.

All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission in writing of the publishers.

All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

Medical knowledge and practice change constantly. This book is designed to provide accurate, authoritative information about the subject matter in question. However, readers are advised to check the most current information available on procedures included and check information from the manufacturer of each product to be administered, to verify the recommended dose, formula, method and duration of administration, adverse effects and contraindications. It is the responsibility of the practitioner to take all appropriate safety precautions. Neither the publisher nor the author(s)/editor(s) assume any liability for any injury and/or damage to persons or property arising from or related to use of material in this book.

This book is sold on the understanding that the publisher is not engaged in providing professional medical services. If such advice or services are required, the services of a competent medical professional should be sought.

Every effort has been made where necessary to contact holders of copyright to obtain permission to reproduce copyright material. If any have been inadvertently overlooked, the publisher will be pleased to make the necessary arrangements at the first opportunity.

Inquiries for bulk sales may be solicited at: jaypee@jaypeebrothers.com

Critical Care

First Edition: **2016**

ISBN: 978-93-5152-213-3

Printed at

by mansdocs.com

Dedicated to

My wife Dr Neena Rungta, children Arpita and Jay and to the contributors of the book. Without them this book would not have been there.

Narendra Rungta

My parents who have given me great values and have always been my pillars of strength and to my patients who have given me the opportunity to evolve as a clinician.
I express my gratitude to my wife Maitree and kids Anirud and Dhruv for supporting me during this project.

Rajesh Pande

by mansdocs.com

Contributors

Diptimala Agarwal MD
Consultant Anesthesiologist Intensivist
OXIM Anesthesia and Critical Care
Associate, Agra, Uttar Pradesh, India

Vandana Agarwal MD FRCA
Associate Professor
Anesthesiology and Critical Care
Tata Memorial Hospital
Mumbai, Maharashtra, India

Vimal K Agarwal MS MCH
Consultant Neurosurgeon
BLK Superspeciality Hospital
New Delhi, India

Armin Ahmed MD PDCC
Research Fellow
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Nayana Amin MD
Associate Professor
Anesthesiology and Critical Care
Tata Memorial Hospital
Mumbai, Maharashtra, India

Pravin Amin MD FCCM
Physician Intensivist
Bombay Hospital
Institute of Medical Sciences
Mumbai, Maharashtra, India

Rahul Kumar Anand MD
Attending Consultant
Department of Critical Care Medicine
Max Superspeciality Hospital
Patparganj, New Delhi, India

Mullai Baalaaji AR MD DM
Senior Resident
Department of Pediatrics
Advanced Pediatric Centre, PGIMER
Chandigarh, Punjab, India

Rohini Arora MD IDCCM
Senior Resident
Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Afzal Azim MD PDCC FICCM
Additional Professor
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Khusrav Bajan MD EDIC
Consultant
Physician and Intensivist
Department of Medicine and Critical Care, PD Hinduja Hospital
Mumbai, Maharashtra, India

AK Baronia MD
Professor and Head
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Anupam Basumatari MD IDCCM
Consultant
Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Yogesh Batra MD DM
Director
Gastroenterology and Hepatology
BLK Superspeciality Hospital
New Delhi, India

Rajesh Bhagchandani MD
Consultant Intensivist
Apex Hospital
Bhopal, Madhya Pradesh, India

Ashish Bhalla MD
Additional Professor
Department of Internal Medicine
PGIMER
Chandigarh, Punjab, India

Manish Bharti MD
Fellow in Critical Care
Indraprastha Apollo Hospital
New Delhi, India

Kapil Borawake MD
Consultant critical care
Prayag hospital
Pune, Maharashtra, India

Sati Chakrabarti MSC PhD
Director Nursing
Medica Superspeciality Hospital Kolkata
West Bengal, India
CCNS Chairperson, Eastern Zone

Anamika Chaudhary DA IDCCM
Associate Consultant
Department of Critical Care
Jeevan Rekha Critical Care and Trauma Hospital
Jaipur, Rajasthan, India

Dhruva Chaudhry MD DNB DM FICP FICCM
Dean Faculty of Medical Superspeciality
Senior Professor and Head PCCM
University of Health Sciences
Rohtak, Haryana, India

Rajesh Chawla MD EDIC EDRM FICCM FCCM
Chancellor
Indian College of Critical Care Medicine
Ex-President
Indian Society of Critical Care Medicine
Senior Consultant
Respiratory Medicine and Critical Care
Indraprastha Apollo Hospital
New Delhi, India

TD Chugh FAMS MD PhD FRCPath (London) FAAM
Emirtus Professor, National Academy of Medical Sciences, India
Ex-Professor and Head PGIMS
Rohtak, Haryana, India

Avijatri Datta
Senior Manager—Clinical Research
Member Secretary—CREC
Senior Registrar—MICC
Medical Superspeciality Hospital
Kolkata, West Bengal, India

Pratibha Dileep MD
Director
Department of Critical Care and Emergency Medicine
Sterling Hospital
Ahmedabad, Gujarat, India

by mansdocs.com

Subhal Dixit MD IDCCM FICCM
Director
Critical Care
Sanjeevan and MJM Hospital
Pune, Maharashtra, India

Harjit Dumra MD
Senior Consultant
Pulmonology and Critical Care
Sterling Hospital
Ahmedabad, Gujarat, India

Mohammad Omar Faruq MD
Professor of Critical Care Medicine
Birden General Hospital and
Ibrahim Medical College
Dhaka, Bangladesh
President, BSCCM

Ashish Garg MD
DNB Fellow in Gastroenterology
Department of Gastroenterology and
Hepatology
BLK Superspeciality Hospital
New Delhi, India

Neeru Gaur DA IDCCM
Associate Consultant
Department of Critical Care
Jeevan Rekha Critical Care and
Trauma Hospital
Jaipur, Rajasthan, India

Supradip Ghosh MD DNB MNAMS EDIC
Senior Consultant and Head
Department of Critical Care Medicine
Fortis Escorts Hospital
Faridabad, Haryana, India

Manoj K Goel MD Diploma in
Interventional Pulmonology
Director
Pulmonology and Sleep Medicine
FMRI, Gurgaon, Haryana, India

Palepu B Gopal MD FRCA CCST FICCM
Senior Consultant
Critical Care Medicine
Care Hospitals
Director, Axon Criticare
Hyderabad, Andhra Pradesh, India

Deepak Govil MD FICCM FCCM EDIC
Associate Director
Institute of Critical Care Medicine
Medanta, The Medicity
Gurgaon, Haryana, India

Abhinav Gupta MD DNB FNB EDIC
Additionl Medical Superintendent
Head—Critical Care and Emergency
School of Medical Sciences and
Research
Sharda University
Greater Noida, Uttar Pradesh, India

Babita Gupta MD
Associate Professor
Trauma Anesthesia and Critical Care
JP Apex Trauma Center
AIIMS, New Delhi, India

Manish Gupta MD FNB
Senior Consultant
Department of Critical Care Medicine
Max Superspeciality Hospital
Patparganj, New Delhi, India

Mukesh Kumar Gupta MD FNB
Senior Consultant
Institute of Critical Care and
Anesthesiology
Medanta the Medicity
Gurgaon, Haryana, India

Mukesh M Gupta MD DM
Senior Consultant in
Neurointensive Care
BLK Superspeciality Hospital
Patparganj, New Delhi, India

Rakesh Gupta MD EDIC
Senior Consultant
Respiratory and Critical Care
Metro Hospitals
Noida, Uttar Pradesh, India

Sachin Gupta MD
Senior Resident
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Vivek Gupta DA DNB MNAMS FACTA
Consultant
Cardiac Anesthesia and
Intensive Care
Hero DMC Hospital
Ludhiana, Punjab, India

Sushma Gurav DNB IDCCM
Consultant Neurotrauma Unit
Grant Medical Foundation
Ruby Hall Clinic
Pune, Maharashtra, India

Mohan Gurjar MD PDCC FICCM
Associate Professor
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Yash Javeri MBBS DA IDCCM
Consultant
Institute of Critical Care Medicine
Max Healthcare
Saket, New Delhi, India

SP Kalantri MD MPH
Director
Professor of Medicine
Department of Internal Medicine
JLN Medical College Wardha
Wardha, Maharashtra, India

Poonam Malhotra Kapoor MD
Professor of Cardiac Anesthesia
AIIMS, New Delhi, India

Arindam Kar MD DNB FNB EDIC
Director
Medica Institute of Critical Care
Medicine
Medica Superspeciality Hospital
Kolkata, West Bengal, India

Pritpal Kaur MD
Attending Consultant
Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Vipin Kauts MD EDIC
Consultant ICU
King Hamad University Hospital
Bahrain, UAE

Puneet Khanna MD IDCCM FCCP
Consultant in Respiratory Medicine
BLK Superspeciality Hospital
New Delhi, India

Khalid Khatib MD
Intensivist and Associate Professor
Department of Medicine
SK Nalve Medical College and General
Hospital
Pune, Maharashtra, India

Parveen Khilnani MD FCCM
Director Pediatric Critical Care
BLK Superspeciality Hospital
New Delhi, India

by mansdocs.com

Gaurav Kochhar MD
Consultant Intensivist
New Delhi, India

Amol Kothekar MD
Assistant Professor, Intensive Care Medicine, Advanced Center for Treatment Research and Education in Cancer (ACTREC), TMH
Mumbai, Maharashtra, India

Lakshmi N Kottu MBBS HCM
Diploma in Cardiology, Institute of Cardiology, Medanta, The Medicity
Gurgaon, Haryana, India

Prashant Kumar MD IDCCM
Fellow, Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

R Ramesh Kumar MD DNB Fellow PICU (IAP) DM
Department of Pediatrics
Advanced Pediatric Centre, PGIMER
Chandigarh, Punjab, India

Saptharishi LG MD DM
Senior Resident
Department of Pediatrics
Advanced Pediatric Centre, PGIMER
Chandigarh, Punjab, India

Vikas Loomba MD
Assistant Professor
Department of Internal Medicine
PGIMER
Chandigarh, Punjab, India

Vinay Malhotra MD DM
Professor and Head
Department of Nephrology
SMS Medical College
Jaipur, Rajasthan, India

RK Mani MD MRCP FICCM
Director, Department of Pulmonology Critical Care and Sleep Medicine
Saket City Hospital
New Delhi, India
Editor, Indian Journal of Critical Care Medicine

Rungmei Marak MD
Additional Professor
Department of Microbiology
SGPGIMS
Lucknow, Uttar Pradesh, India

Vikas Maurya MD FNB EDIC FCCP
Consultant in Respiratory Medicine
BLK Superspeciality Hospital
New Delhi, India

Mir Faisal Mazid MBBS DNB
Clinical Associate
Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Yatin Mehta MD MNAMS FRCA FAMS FIACTA FTEE FISCCM
Chairman, Institute of Critical Care and Anesthesiology
Medanta the Medicity
Gurgaon, Haryana, India

Rajesh Chandra Mishra MD FNB EDIC FCCP
Consultant Intensivist
Ahmedabad, Gujarat, India

Chander Mohan SM MBBS MD FICR FIAMS FIMSA FEISI FICGP MNAMS
PDCC Radiodiagnosis Oncology
Post Doctoral Training Vascular and Interventional Radiology
Director
Intervention Radiology
BLK Superspeciality Hospital
New Delhi, India

Krishna Prasad Mulavisala MD FRCA CCST
Senior Consultant and Head
Cardiac Anesthesia
Care Hospitals
MD Axon Anesthesia Services
Hyderabad, Andhra Pradesh, India

Manish Munjal MD FICCM
Vice President
Jeevan Rekha Critical Care and Trauma Hospital
Jaipur, Rajasthan, India

Sheila Nainan Myatra MD FICCM
Professor of Anesthesia and Intensive Care
Tata Memorial Hospital
Mumbai, Maharashtra, India

Monish Nakra MD
Colonel and Senior Advisor
Anesthesiology and Critical Care
Northern Command Hospital
Udhampur, Jammu & Kashmir, India

Prashant Nasa MD FNB IDCCM EDIC FICCM FCCP
Senior Intensivist and Co-ordinator
Critical Care and Emergency Medicine
Shri Balaji Action Medical Institute
New Delhi, India

Vaibhav Kumar Nasa MD
Consultant Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Sanjay Kumar Nihlani MD
Associate Consultant
Department of Critical Care Medicine
Max Superspeciality Hospital
Patparganj, New Delhi, India

Maitree Pande MD
Professor of Anesthesiology
Lady Hardinge Medical College
New Delhi, India

Rajesh Pande MD PDCC (SGPGIMS) FICCM FCCM (USA)
Director
Critical Care and Emergency Medicine
BLK Superspeciality Hospital
New Delhi, India

Sunil P Pandya MD PDCC
Head, Department of Anesthesiology Pain and Critical Care
Fernandez Hospital
Hyderabad, Andhra Pradesh, India

Sauren Panja MD FNB
Co-ordinator Critical Care and Head Internal Medicine
Medica Superspeciality Hospital
Kolkata, West Bengal, India

Shikha Panwar MD
Consultant Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Atul Pathak MBBS DA
Clinical Associate and IDCCM Fellow
Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Vijaya P Patil MD DA
Professor, Anesthesiology and Critical Care, Tata Memorial Hospital
Mumbai, Maharashtra, India

by mansdocs.com

JV Peter MD
Professor
Department of Critical Care Medicine
Christian Medical College
Vellore, Tamil Nadu, India

R Pratheema MD IDCCM
Consultant in Critical Care
Apollo Hospital, Chennai, India

Girish Rajpal MS MCH
Consultant, Neurosurgeon
BLK Superspeciality Hospital
New Delhi, India

N Ramakrishnan AB (Int Med) AB (Crit Care) AB (Sleep Med) MMM FACP FCCP FCCM FICCM
Vice Chancellor
Indian College of
Critical Care Medicine
President
Indian Sleep Disorders Association
Director, Critical Care Services
Senior Consultant in Critical Care and Sleep Medicine
Chennai Critical Care Consultants (CCCC)
Apollo Hospitals, Chennai, India

Suresh Ramasubban AB (CCM) FCCP
Senior Consultant
Department of Critical Care Medicine
Apollo Gleneagles Hospital
Kolkata, West Bengal, India

V Ruth Adora Rao
Critical Care Co-ordinator
Medical Superspeciality Hospital
Kolkata, West Bengal, India

Rajul Rastogi MBBS, MD (Radiodiagnosis) MNAMS FIMSA FICRI
Assistant Professor
Department of Radiodiagnosis
Teerthanker Mahaveer
Medical College and
Research Center
Moradabad, Uttar Pradesh, India

Narendra Rungta MD FISCCM FCCM FICCM
President—Indian Society of
Critical Care Medicine
Association of SAARC
Critical Care Societies
Jeevan Rekha Critical Care and
Trauma Hospital
Jaipur, Rajasthan, India

Neena Rungta MD
Ex-Professor and Vice President
Jeevan Rekha Critical Care and
Trauma Hospital
Jaipur, Rajasthan, India

Samir Sahu MD
Senior Consultant
Pulmonary and Critical Care
Apollo Hospital
Bhubneshawar, Odisha, India

Srinivas Samvedam MD
Consultant and Head
Department of Critical Care Medicine
Care Hospital
Hyderabad, Andhra Pradesh, India

Utpal Sarma MD
Consultant Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Prashant Saxena MD
Senior Consultant
Department of Pulmonology Critical
Care and Sleep Medicine
Saket City Hospital
New Delhi, India

R Senthilkumar MD IDCCM EDIC
Senior Consultant in Critical Care
Apollo Hospital
Chennai, Tamil Nadu, India

Pinak Ashok Shrikhande MD FNB
Director, Fortis Hospital
Vasant Kunj and Shalimar Bagh
New Delhi, India

Ajeet Singh MD IDCCM Fellow
Department of Critical Care Medicine
PGIMER, Rohtak, Haryana, India

Balbir Singh MD DM FACC
Chairman, Division of Electrophysiology
Institute of Cardiology
Medanta, The Medicity
Gurgaon, Haryana, India

DK Singh MD FICCM
Professor in Trauma and
Emergency Medicine
AIIMS, Bhopal, India

Manoj Singh MD DNB FCCP FNB
Consultant Critical Care
Apollo Hospitals International Limited
Ahmedabad, Gujarat, India

RK Singh MD PDCC FICCM
Associate Professor
Department of Critical Care Medicine
SGPGIMS
Lucknow, Uttar Pradesh, India

Yogendra Partap Singh MD
Senior Consultant and Head
Department of Critical Care Medicine
Max Superspeciality Hospital
Patparganj, New Delhi, India

Amit Kumar Singhal MD
Senior Consultant
Liver and Hepatobiliary Anesthesia
BLK Superspeciality Hospital
New Delhi, India

Sunit Singhi MD FIAP FAMS FISCCM FICCM FCCM
Professor and Head
Department of Pediatrics
Advanced Pediatric Centre, PGIMER
Chandigarh, Punjab, India

Mehul Solanki MD
Spectrum Associates
Department of Critical Care Medicine
Apollo Hospital
Ahmedabad, Gujarat, India

Shrikanth Srinivasan MD DNB FNB EDIC
Consultant
Institute of Critical Care
Medanta the Medicity
Gurgaon, Haryana, India

Akhil Taneja MD IDCCM
Department of Critical Care Medicine
Max Superspeciality Hospital
Patparganj, New Delhi, India

George M Varghese MD DNB DTH &M
Professor
Department of Infectious Disease
Christian Medical College
Vellore, Tamil Nadu, India

Abhishek Vishnu MD
Consultant Critical Care Medicine
BLK Superspeciality Hospital
New Delhi, India

Kapil Zirpe MD
Director and Head Neurotrauma Unit
Grant Medical Foundation
Ruby Hall Clinic
Pune, Maharashtra, India

by mansdocs.com

Foreword

It gives me a great pleasure to write the foreword to this new book on *Critical Care*.

Whenever a new book on *Critical Care* arrives, the simplest question asked is "Do we need another book on this subject"? It is natural that a reader's first reaction could be this. It must be emphasized that there is a dearth of books on *Critical Care* with an all Indian Authorship. From this perspective, it is nice to welcome this new book in the libraries of all concerned.

Critical Care as a discipline has grown in India in leaps and bounds over the last two decades. It is thus natural that this book will be in demand. Unfortunately, due to constraints of time, I could not go through the actual contents of the articles. This is really an impressive list of topics and the Editors need to be complimented for the same. The authors list is also impressive and consists of experienced and knowledgeable consultants in the field of *Critical Care* in India. One hopes that the contents of the article are as impressive and help the readers in their quest of appropriate knowledge.

Critical Care is expanding and evolving very rapidly. Along with the science of evidence we need the wisdom of experience in dealing with situations which threaten life. One sincerely hopes that books like this keep an important balance in providing the information and insight into the challenging world of this fascinating specialty of Medicine.

Shirish Prayag MD FCCM
Ex-President, Indian Society of Critical Care Medicine
Managing Director and Chief Consultant
Critical Care Medicine
Prayag Hospital
Pune, Maharashtra, India

by mansdocs.com

Preface

During the last decade, intensive care in India has matured, gained tremendous experience and come of age. The momentum generated during the previous years has made us realize the need of a major Indian textbook in Critical Care Medicine, authored by young Indian intensivists, since we have mostly depended on western literature for our academic needs. We are certain that this book *Critical Care* would be lucid, readable, emphasize on practical aspects and serve as a basic specialty book on Critical Care in India. Eminent critical care physicians from India's top hospitals and institutions have contributed to the book. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India, has been kind enough to facilitate this project.

Efforts have been made to include certain topics that are relevant to India like poisoning, tropical infections, end-of-life care and pregnancy-related issues. We have also tried to cover the practical aspects of mechanical ventilation for the readers. We are hopeful that the book would provide the essential information not only to the postgraduate students but will also be useful to the practicing intensivists in India. We express our gratefulness to Dr Shirish Prayag, a Doyen in Critical Care in India for writing the Foreword for this book. We also express our heartfelt gratitude to all the contributors for giving us their high quality manuscripts in time. We hope you will enjoy reading it !

Narendra Rungta
Rajesh Pande
Manish Munjal
Sudhir Khunteta

by mansdocs.com

Acknowledgments

We appreciate the contribution of the Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India in making this project a success. In particular mention are Mr Jitendar P Vij (Group Chairman), Mr Ankit Vij (Group President) and Ms Chetna Malhotra Vohra (Associate Director) for their belief in our groups' ability to deliver and Ms Saima Rashid (Project Manager) who did very well in making sure we catch up with the deadline.

by mansdocs.com

Contents

Section 1: General

1. **Assessment of Critically Ill Patients** 3
   Kapil Zirpe, Sushma Gurav
2. **Airway Management in ICU** 9
   Anamika Chaudhary, Manish Munjal, Neeru Gaur, Neena Rungta, Narendra Rungta
3. **Hemodynamic Monitoring in ICU** 23
   Vijaya P Patil, Nayana Amin, Vandana Agarwal
4. **Fluid Balance in Critically Ill Patients** 37
   Shikha Panwar
5. **Vasopressors and Inotropes** 46
   Poonam Malhotra Kapoor
6. **Multiple Organ Dysfunction Syndrome** 57
   R Pratheema, R Senthilkumar, N Ramakrishnan
7. **Cardiopulmonary Resuscitation: A Paradigm Shift** 64
   Khusrav Bajan
8. **Therapeutic Hypothermia** 70
   Pinak Ashok Shrikhande
9. **Management of Organ Donor** 75
   Rajesh Pande
10. **Scoring Systems in ICU** 79
    Avijatri Datta, Arindam Kar, Sauren Panja
11. **Guidelines for ICU Planning and Designing in India** 87
    Narendra Rungta, Neena Rungta, Manish Munjal, Neeru Gaur, Anamika Chaudhary
12. **Guidelines and Protocols in ICU** 94
    Manoj Singh, Mehul Solanki
13. **Clinical Audit and Handoff in ICU** 98
    Mohammad Omar Faruq
14. **Critical Care Nursing in India** 104
    Arindam Kar, Sati Chakrabarti, V Ruth Adora Rao, Manish Munjal, Neena Rungta, Narendra Rungta

Section 2: Cardiac Care

15. **Acute Coronary Syndrome** 111
    Suresh Ramasubban

by mansdocs.com

16. **Heart Failure** 117
Yatin Mehta, Mukesh Kumar Gupta

17. **Cardiac Arrhythmias in ICU** 129
Supradip Ghosh

18. **Hypertensive Emergency** 145
Yatin Mehta, Mukesh Kumar Gupta

19. **Pacing in the ICU Setting** 154
Balbir Singh, Lakshmi N Kottu

20. **Pulmonary Embolism** 160
Rajesh Chawla, Manish Bharti

21. **Intensive Care Unit Management of Patients with Right Heart Failure** 169
Harjit Dumra

Section 3: Respiratory Care

22. **Community Acquired Pneumonia** 183
Rajesh Pande, Mir Faisal Mazid

23. **Ventilator-Associated Pneumonia** 190
Manoj K Goel

24. **Acute Respiratory Distress Syndrome** 195
Rajesh Pande, Vipin Kauts

Section 4: Liver and Digestive System

25. **Acute Liver Failure** 203
Utpal Sarma, Vaibhav Kumar Nasa, Amit Kumar Singhal

26. **Acute Pancreatitis** 216
Yogesh Batra, Ashish Garg

27. **Hepatorenal and Hepatopulmonary Syndromes** 226
Rajesh Pande

28. **Anesthesia for Liver Transplantation** 233
Vaibhav Kumar Nasa, Utpal Sarma, Amit Kumar Singhal

29. **Critical Care Aspects in Adult Liver Transplantation** 253
Shrikanth Srinivasan, Deepak Govil

Section 5: Renal Care

30. **Diagnosis of Acute Kidney Injury** 263
Vinay Malhotra

31. **Renal Replacement Therapy** 267
Rajesh Pande

by mansdocs.com

32. Critical Care Management of Renal Transplant Recipients 273
Sachin Gupta, Deepak Govil

33. Acid-Base Disorders in Critical Care 276
Palepu B Gopal, Krishna Prasad Mulavisala

34. Disorders of Potassium 289
Yogendra Pratap Singh, Sanjay Kumar Nihlani, Rahul Kumar Anand

35. Sodium Disorders 296
Yogendra Pratap Singh, Manish Gupta, Akhil Taneja

36. Disorders of Calcium and Magnesium 306
Khalid Khatib, Subhal Dixit, Kapil Borawake

Section 6: Neurological Care

37. Management of Critically Ill Trauma Patients 313
Babita Gupta

38. Management of Spinal Injury 329
Samir Sahu

39. Neurocritical Care Management of Subarachnoid Hemorrhage 337
Mukesh M Gupta, Vimal K Agarwal, Girish Rajpal

40. Intensive Care Management of Postoperative Neurosurgical Patients 346
Mukesh M Gupta

Section 7: Obstetric Critical Care

41. Physiology of Pregnancy 357
Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

42. Respiratory Disorders During Pregnancy 364
Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

43. Liver Disease Complicating Pregnancy 369
Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

44. Peripartum and Postpartum Intensive Care in Pregnancy 372
Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

Section 8: Pediatric Critical Care

45. Recognition and Assessment of Critically Ill Child 381
Praveen Khilnani

46. Pediatric Septic Shock 387
Saptharishi LG, Sunit Singhi

47. Status Epilepticus 398
Mullai Baalaaji AR, Sunit Singhi

by mansdocs.com

48. **Raised Intracranial Pressure in Children with an Acute Brain Injury: Monitoring and Management** 406
R Ramesh Kumar, Sunit Singhi

Section 9: Infections

49. **Extended Spectrum Beta Lactam Producing Infections in Intensive Care Unit** 421
Afzal Azim, AK Baronia

50. **Infections in Immunocompromised Patients in ICU** 427
AK Baronia, Afzal Azim, RK Singh

51. **Invasive Fungal Infections in Critically Ill Patients** 434
AK Baronia, Armin Ahmed, Afzal Azim, Mohan Gurjar, Rungmei Marak

52. **Febrile Neutropenia** 443
Rajesh Pande

53. **Fever in the ICU** 448
Rajesh Pande

54. **Cytomegalovirus Infection in Critically Ill Patients** 454
Armin Ahmed, Afzal Azim, Mohan Gurjar, AK Baronia

55. **Tropical Infections in ICU** 456
Prashant Nasa, Dhruva Chaudhry

56. **Tropical Fever—Management Guidelines ISCCM Tropical Fever Group** 465
Sunit Singhi, Dhruva Chaudhary, George M Verghese, Ashish Bhalla, SP Kalantri, JV Peter, Rajesh Chandra Mishra, Rajesh Bhagchandani, TD Chugh, Narendra Rungta, Manish Munjal

Section 10: Ethics and End-of-Life Care Issues

57. **Bioethical Considerations** 475
RK Mani, Prashant Saxena

58. **End-of-Life Care Practices in the World** 478
RK Mani, Prashant Saxena

Section 11: Miscellaneous

59. **Burns, Inhalation and Electrical Injury** 483
Diptimala Agarwal

60. **Diabetic Ketoacidosis** 494
DK Singh

61. **Oncological Emergencies** 498
Sheila Nainan Myatra, Amol Kothekar

62. **Post-cardiac Arrest Syndrome** 508
Yash Javeri

by mansdocs.com

63. Intra-abdominal Hypertension and Abdominal Compartment Syndrome 516
Rajesh Pande, Puneet Khanna

64. Nutrition in a Critically Ill Patients 521
Pravin Amin

65. Approach to an Unknown Poisoning 525
Vikas Loomba, Ashish Bhalla

66. Specific Intoxications 531
Ajeet Singh, Dhruva Chaudhry

67. Fatal Envenomations 543
Prashant Kumar, Dhruva Chaudhry

68. Care of Obese Patient in ICU 550
Gaurav Kochhar, Abhinav Gupta

69. Imaging in Intensive Care Unit 555
Chander Mohan, Rajul Rastogi

Section 12: Mechanical Ventilation

70. Respiratory Mechanics: Basics 569
Rajesh Pande, Vipin Kauts

71. Principles of Mechanical Ventilation 573
Rajesh Pande, Maitree Pande

72. Basic Modes of Ventilation 576
Maitree Pande, Rohini Arora

73. Ventilator Graphics 580
Rajesh Pande, Puneet Khanna

74. Newer Modes of Ventilation 587
Rajesh Pande, Vipin Kauts

75. Weaning/Liberation from Mechanical Ventilation 592
Rajesh Pande, Monish Nakra

76. Non-Invasive Ventilation 596
Rajesh Pande, Rakesh Gupta

77. Ventilation Strategy in Obstructive Airway Disease 602
Rajesh Pande, Atul Pathak

78. Ventilation Strategy in Trauma 605
Vikas Maurya

79. Rescue Strategies in ARDS—Recruitment Maneuvers 610
Rajesh Pande, Anupam Basumatari

80. Rescue Therapy in ARDS: Prone Ventilation and High Frequency Oscillation Ventilation (HFOV) 613
Rajesh Pande, Abhishek Vishnu

by mansdocs.com

81. Extracorporeal Membrane Oxygenation **616**
Rajesh Pande, Vivek Gupta, Abhishek Vishnu

82. Aerosol Delivery Systems in Mechanical Ventilation **621**
Rajesh Pande, Pritpal Kaur

APPENDICES

Appendix 1: Hemodynamic Formulae and Values **627**

Appendix 2: Respiratory Formulae and Values **629**

Appendix 3: Acid-Base Balance, Renal Formulae and Values **631**

Appendix 4: Scoring System Used in ICU **633**

Appendix 5: Spectrum of Commonly Used Antibiotic in ICU **636**

Index *637*

by mansdocs.com

SECTION 1

General

by mansdocs.com

CHAPTER

1

Assessment of Critically Ill Patients

Kapil Zirpe, Sushma Gurav

INTRODUCTION

- Critical illness is a life-threatening process.
- Failure of early detection of disordered physiology and the establishment of early appropriate preventative measures leads to:
  - Unplanned admissions to intensive care.
  - Multiorgan failure
  - Unnecessary deaths.
- Simple appropriate treatments and calling early for help will avoid about 40% of intensive care unit (ICU) admissions and improve outcome, e.g. early administration of antibiotics in patients with an infective cause, e.g. meningitis, pneumonia, septic shock etc.
- Ideal management involves prediction of at risk patients, proactive observation and timely intervention.

Critical illness is preceded by a period of physiological deterioration, but studies reveal that the early signs of this are frequently missed by healthcare professionals. Signs and symptoms can be misleading and patients may compensate for a long time for abnormal changes in their physiology (Table. 1). Hence, the gradually deteriorating patient on a hospital ward may go unnoticed until severe organ failure is established. *Chain of response* is recently published guidance for recognizing critically ill patients. It requires accurate recording and documentation of vital signs, recognition and interpretation of abnormal values and appropriate patient assessment and intervention. If conducted in a correct and effective, timely manner, it ensures the right patient receives the right treatment at the right time.

Regardless of who assesses the patient, a systematic ABCDEF approach should be used (Fig. 1). This facilitates assessment and correction of life-threatening problems by priority, provides a standardized approach between professionals, aids communication and reduces the risk of missing important details. In the initial stages, primary assessment, resuscitation and life-saving interventions should be performed concurrently.

Table 1: Early warning scoring system—chain of response. A score of 5 or more is associated with admission to intensive care unit or increased likelihood of death. Abnormal score prompt us to increase frequency of observations and urgent review by qualified professionals.

Score	*1*	*2*	*3*	*0*	*1*	*2*	*3*
Systolic blood pressure	<45% ↓	30% ↓	15% ↓	Normal for patient	15% ↑	30% ↑	45% ↑
Heart rate	–	<40	41–50	51–100	101–110	111–129	>130
Respiratory rate	–	<9	–	9–14	15–20	21–29	>30
Temperature (°C)	–	<35	–	35.0–38.4	–	>38.5	–
AVPU	–	–	–	Alert	Voice	Pain	Unresponsive

(AVPU: Alert, voice, pain, unresponsive).

by mansdocs.com

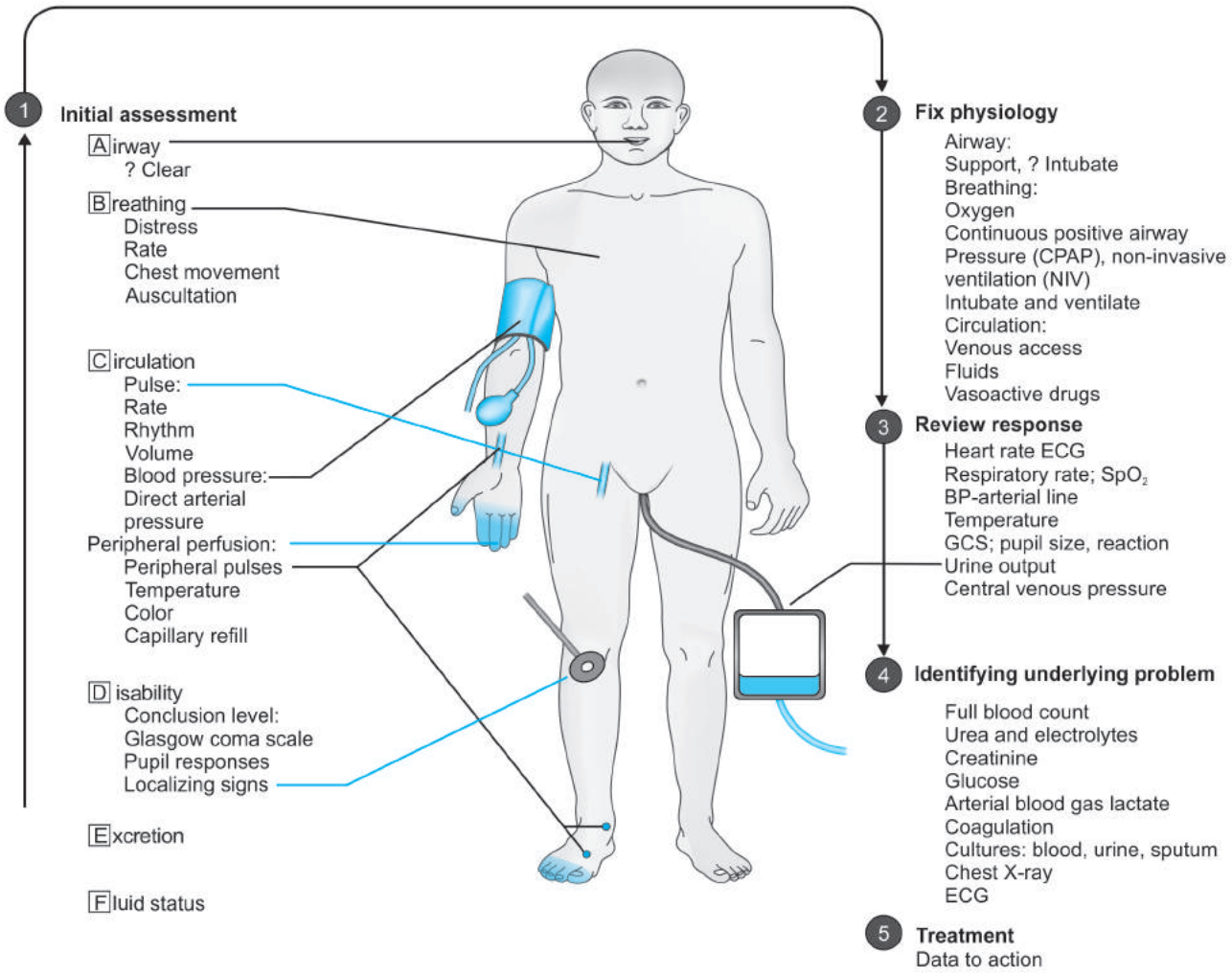


Fig. 1: A systemic ABCDEF assessment approach for critically ill patient.

OBJECTIVES

- *Change of approach*: Traditional linear verses new iterative
- *Fix physiology*
  - *Initial assessment*: ABCDEFG approach (Fig. 1)
  - Immediate management
- *Monitoring*: Review response
- *Investigations*: Identifying underlying problem
- *Treatment*: Turning data into effective action.

CHANGE OF APPROACH

Traditional linear approach:

- History
- Examination
- Investigation
- Diagnosis
- Treatment

New iterative approach:

- Fix physiology
- Review response
- Short history, examination, tests
- Preliminary diagnosis

FIX PHYSIOLOGY

Airway (Patency/Securing of Airway)

A fast, simple way of assessing the airway is to ask a question, such as "how are you?"/what is your name? A clear, coherent answer implies a patent airway, sufficient respiratory capacity to permit speech and adequate cerebral perfusion for cognitive processing.

by mansdocs.com

If there is risk of cervical spine injury, manual in-line stabilization should be maintained and in the acute setting high-flow oxygen should be administered to all patients and titrated to achieve a SpO_2 94–98%. Thorough airway assessment should use the "look, listen, feel" approach.

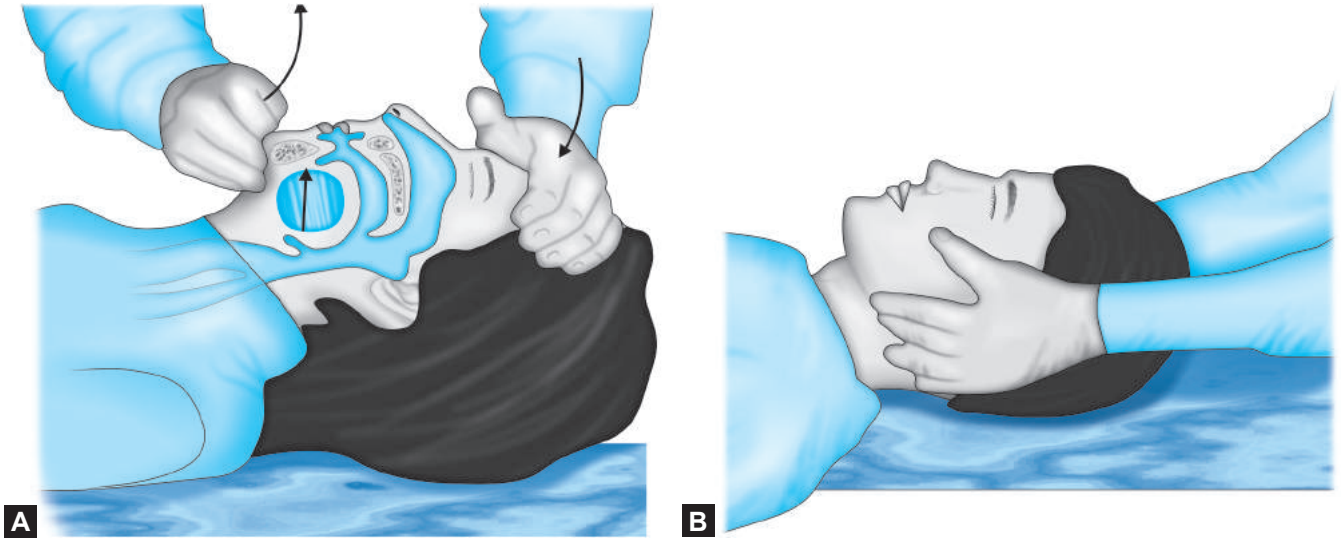
- *Look* for tachypnea, sweating, use of accessory muscles, see-saw thoracoabdominal movements and recession.
- *Listen* for gurgling or stridor. Note that stridor may be absent, particularly, in severe cases and the presence of normal oxygen saturation does not exclude a compromised airway.
- *Feel* for gush of air.

Airway obstruction must be corrected immediately. A patient with infectious (e.g. epiglottitis) and inflammatory (e.g. burns, anaphylaxis) causes rapidly progressive and life-threatening of airway obstruction. Head tilt and chin lift can be used to achieve airway patency in unconscious patients with no suspected cervical spine injury (Fig. 2A). Jaw thrust and manual in-line stabilization may be applied in patients with cervical trauma (Fig. 2B). A conscious, the patient often adopt the best position to maintain their airway (usually sitting upright and leaning forward). Never attempt to lay such a patient flat this may precipitate complete obstruction. Early request for anesthetist help can be lifesaving.

Breathing (Respiratory Rate, SpO_2, Arterial Blood Gas, Types of Respiratory Failure)

Marked tachypnea is a useful marker of a respiratory pathology but is also a sensitive early indicator of acute illness, occurring as the body attempts to correct metabolic acidosis secondary to poor tissue perfusion. Although peripheral oxygen saturations should be recorded, it can be unreliable and falsely reassuring; it does not assure adequate ventilation. Arterial blood gas with lactates analysis should be done if time permits.

Differentiating between the two types of respiratory failure can help in reaching diagnosis and management (Flowchart 1). In mismatch condition, just increasing the FiO_2 (fraction of inspired oxygen) may not correct hypoxemia. In severe cases, type I respiratory failure may progress to type II failure as fatigability, hypoxia and acidosis may cause muscle weakness. This requires urgent consideration of invasive ventilation. Patients with advanced chronic obstructive pulmonary disease often display chronic type II respiratory failure, with compensation of hypercarbia through renal bicarbonate retention. In these patients, arterial acidemia is a more sensitive marker of acute deterioration than absolute $PaCO_2$ value. In type II respiratory failure, increasing the FiO_2 will improve hypoxemia but correction of hypercarbia needs an increase in alveolar ventilation and treatment of the underlying cause.

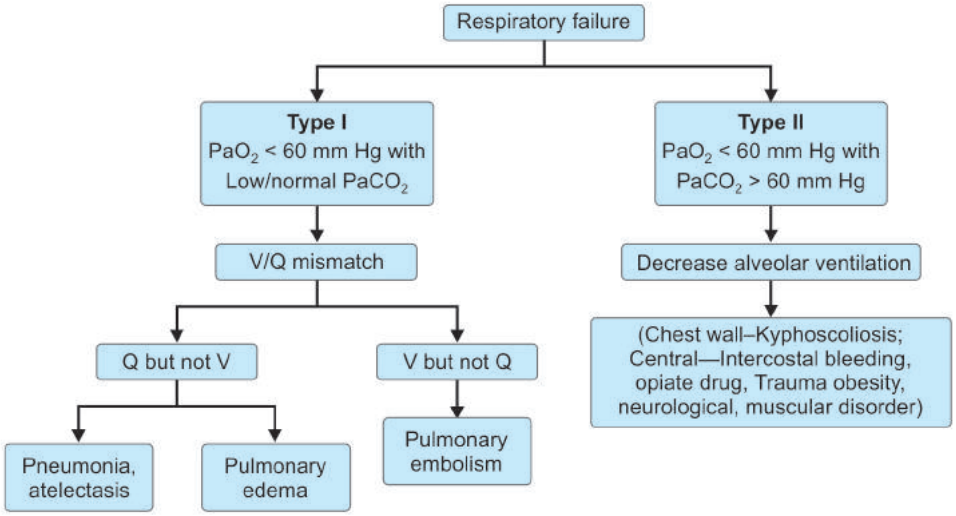


Head-Tilt, Chin-Lift Jaw Thrust

Figs. 2A and B: (A) Head-tilt, chin-lift (for medical patients without spinal injury). (B) Jaw thrust (for trauma patients or those with unknown nature of illness maintain spinal immobilization).

by mansdocs.com

Flowchart 1: Differentiation between the types of respiratory failure.



Early consideration for continuous positive airway pressure (CPAP), non invasive ventilation (NIV), or invasive ventilation for patients who do not improve with oxygenation therapy with oxygen therapy is very helpful.

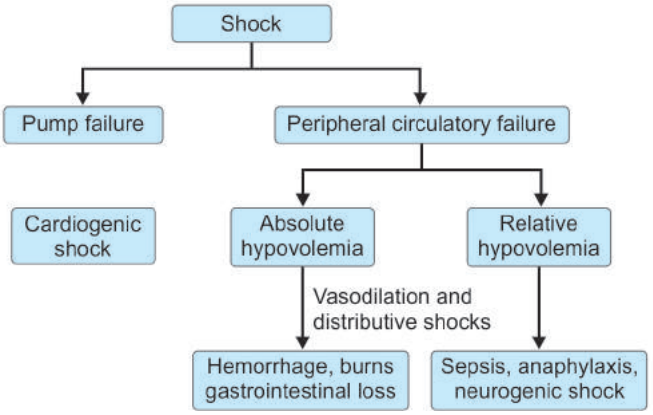
Circulation (Tissue Perfusion, Types of Shock, Pulse Pressure)

Tissue perfusion should be rapidly assessed for circulatory status rather than blood pressure. FOR adequate tissue perfusion presence of an appropriate circulating volume of blood with an adequate pressure is required. Inadequate oxygen supply to organs or tissue to meet the metabolic demands of tissue and organs leads to shock. The causes of shock are shown in Flowchart 2.

The signs of shock vary depending on etiology and are frequently masked in patient like young, fit adults, pregnant women or patients on beta-blockers. Hypoperfusion can occur despite a normal blood pressure and hypotension frequently occurs late and is alarming sign. The blood pressure can provide valuable information: a decrease in diastolic blood pressure can indicate vasodilation in early distributive shock and narrowing of the pulse pressure is a sign of arterial vasoconstriction to maintain perfusion in the condition of decreased cardiac output or hypovolemia. Capillary refill, tachypnea, confusion, agitation and oliguria are the minor signs of end-organ hypoperfusion and should be actively documented.

Hyperlactatemia is a marker of critical illness and associated with increased morbidity and mortality. Early measurement of lactate with sequential monitoring is important for prognostication of clinical outcomes.

Flowchart 2: Causes of shock.



Assessment of Disability and Drug (AVPU Score)

The patient's neurological status should be assessed using the Glasgow Coma Scale and AVPU score. In critically ill patient, multiple factors may contribute to depression of the conscious level, e.g. hypoxia, hypercarbia, hypothermia, electrolyte abnormalities, sepsis or metabolic derangement. Detailed neurological examination is unreliable in the presence of systemic illness. A repeat neurological examination should be done once these factors have been corrected.

by mansdocs.com

Look for Neck Rigidity Exclude hypoglycemia and consider the influence of alcohol, oral hypoglycemic drugs and other toxins. Review the drugs taken by the patient. Is the present condition because of them? Specially, sedatives, antihypertensive and allergies.

Excretion

The relevant questions are:
- How much is the output?
- When the last urine was passed?
- Review of intake/output chart.
- Is the urine clear?
- Is the bladder palpable?
- Any other source of loss like diarrhea, drains, occults.

Fluid Status and Electrolytes

The relevant questions should focus on:
- How much fluid?
- Which fluid?
- What are the electrolytes?
- Set target values for reevaluation or intervention.

General Examination—Simple and Quick

- Temperature
- Anemia
- Jaundice
- Edema
- Tenderness
- Distention
- Invasive lines sites
- Wounds.

MONITORING: REVIEW RESPONSE

Use multiple parameter or aggregate weighted scoring system. Define the parameter to be measured and frequency of observations (Box 1). State the parameters cutoff points that should trigger a response. The physiological trends should be monitored to assess whether the patient is getting better or worse.

If there is no change in clinical condition with initial treatment, the patient's condition may have deteriorated and now he may need more complex treatment interventions.

Box 1: Parameters to be monitored in a critical patient.

- Heart rate, level of consciousness
- Respiratory rate, oxygen saturation
- Systolic blood pressure, temperature
- Biochemistry (lactate, blood glucose, base deficit, arterial pH)
- Hourly urine output
- Pain

INVESTIGATIONS: IDENTIFYING THE UNDERLYING PROBLEM

In acutely ill patient, the history comes after stabilization of physiology. Make a note of comorbidity and cardiorespiratory reserve (exercise tolerance). The history taking in initial assessment will reveal whether the patient belongs to a difficult to assess group (Box 2).

"Laboratory tests" should be ordered on basis of patient-related history and clinical findings.
- Arterial blood gas, lactate
- Complete blood count
- Electrolytes
- Renal function test/liver function test
- Chest X-ray, extended focused assessment with sonography for trauma
- Electrocardiography
- Blood glucose
- *Culture*: blood culture, urine and sputum

TREATMENT: TURNING DATA INTO EFFECTIVE ACTION

- Making a diagnosis is an essential for the subsequent part of management.
- The diagnosis should be specific.
- Treatment plan should include:
  - *Problem oriented approach*: what is the main problem that needs to be fixed?
  - *Causation*: have I understood the pathology to be treated?

Box 2: Difficult to assess group.

- *Young adults*: Physiological reserve masks signs of severe illness until illness is very advanced. Significant de-arrangement in physiological parameter indicates very severe illness.
- Elderly or immunocompromised patients: Physiological reserve is severely compromised. Compensatory response is damped and hides the signs of severe illness.
- *Trauma patients*: Multiple injuries and distracting pain makes patient notoriously difficult to assess. Mechanism of injury is vital for hypothesis of likely injuries.

by mansdocs.com

- *Therapeutic goals*: what is the goal and how soon to achieve it?
- *Site of care*: which is the best place to treat this patient?
- *Communication*: with the patient, other consultants and the family.

Evidence Tidbits—Top Five Signs of Physiological Deterioration

Early signs: Base deficit –5 to –8 mmol/L, partial airway obstruction, poor peripheral circulation, drain fluid loss > expected and pH < 7.3 but > 7.2.

Late signs: Urine output < 200 mL in 24 hours, pH < 7.2, unresponsive to voice, base deficit, –8 mmol/L and anuric.

BIBLIOGRAPHY

1. National Institute for Health and Excellence. Acutely ill patients in hospital: recognition of and response to acute illness in adults in hospital. London: National Institute for Health and Clinical Excellence; 2007.
2. Reynolds SF, Heffner J. Airway Management of critically ill patient: rapid sequence intubation. Chest. 2005; 127(4):1397-412.
3 Robertson LC, Mohammed Al-Haddad. Recognizing the critically ill patient. Anesth Inten Care Med. 2013;14(1):11-4.

by mansdocs.com

CHAPTER

2

Airway Management in ICU

Anamika Chaudhary, Manish Munjal, Neeru Gaur, Neena Rungta, Narendra Rungta

INTRODUCTION

Airways are devices to ensure open pathway between the mouth and nose and the patient's lungs. Airway management is primary consideration in cardiopulmonary resuscitation, emergency medicine, anesthesia and intensive care medicine. Upper airways obstruction is a life threatening emergency and rapid assessment and establishment of patent airway takes priority. Intensive care unit (ICU) physician should be capable of performing a variety of airway management techniques. Most commonly used techniques are being described below:

Airway Management Techniques

- *Noninvasive (above the glottis)*
  - Oro/nasopharyngeal airways
    - Bag and mask ventilation
    - Combitube
    - Laryngeal mask airway
- *Invasive (through/below glottis)*
  - Nonsurgical
    - Endotracheal intubation (ET)
  - Surgical
    - Tracheostomy
      - Percutaneous
      - Surgical
    - Cricothyroidotomy
      - Percutaneous
      - Surgical.

ANATOMY OF AIRWAYS

Successful intubation, cricothyroidotomy and tracheostomy need detailed knowledge of airway anatomy. There are two openings to airways, mouth and nose leading to oropharynx and nasopharynx respectively (Fig. 1). Oral and nasal cavity are separated by hard and soft palate. The pharynx is a fibromuscular structure extending from skull base up to cricoid cartilage, at the level of opening of esophagus. It is divided into *nasopharynx and oropharynx,* as mentioned above, and *laryngopharynx* (or hypopharynx). It is separated by oropharynx

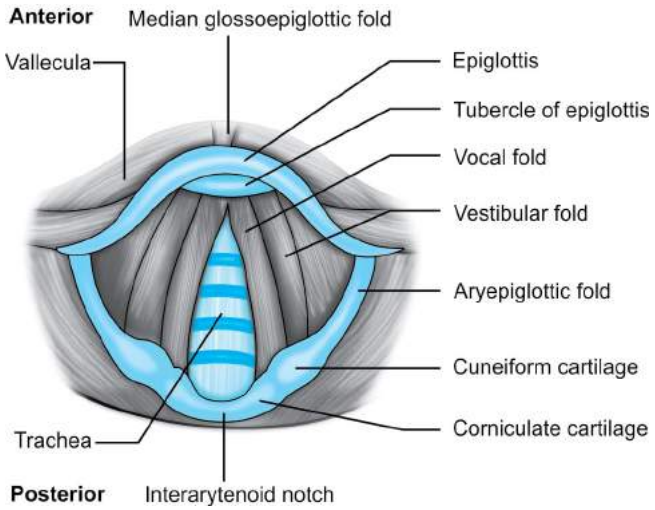


Fig. 1: Laryngoscopic view of the glottic opening.

by mansdocs.com

by epiglottis. Larynx is composed of nine cartilages, which are *unpaired* thyroid, cricoid, epiglottis and *paired* arytenoids, cuneiform and corniculate (Fig. 2).

Nerve Supply

Sensory innervation of the airway is by three cranial nerves trigeminal, glossopharyngeal and nerve. Nose is innervated by V_1 and V_2 branches of trigeminal nerve. V_3 Glossopharyngeal nerves and V_3 branch supply anterior two-thirds and posterior one-third tongue respectively. Pharynx above epiglottis is innervated by ninth nerve and below it by vagus through superior and recurrent laryngeal nerves. Superior laryngeal nerve divides into external and internal laryngeal nerves to supply areas between epiglottis and vocal cords. Recurrent laryngeal nerve supplies larynx below vocal cords and trachea. All muscles of larynx are innervated by recurrent laryngeal nerve except cricothyroid, which is supplied by external laryngeal nerve, a branch of superior laryngeal nerve.

Posterior cricoarytenoid muscles abduct vocal cords and lateral cricoarytenoid muscles are the principal adductors.

Acute bilateral recurrent laryngeal nerve palsy with intact superior laryngeal nerve can result in stridor and respiratory distress because of unopposed tension of cricothyroid muscles.

Blood supply of larynx is derived from branches of superior and inferior thyroid arteries which arise from external carotid artery. Cricothyroid artery arises from superior thyroid artery (which extends along lateral edge of cricothyroid membrane) and crosses upper margin of cricothyroid membrane. So, best approach during cricothyroidotomy is to stay in midline and at midpoint between thyroid and cricoid cartilages.

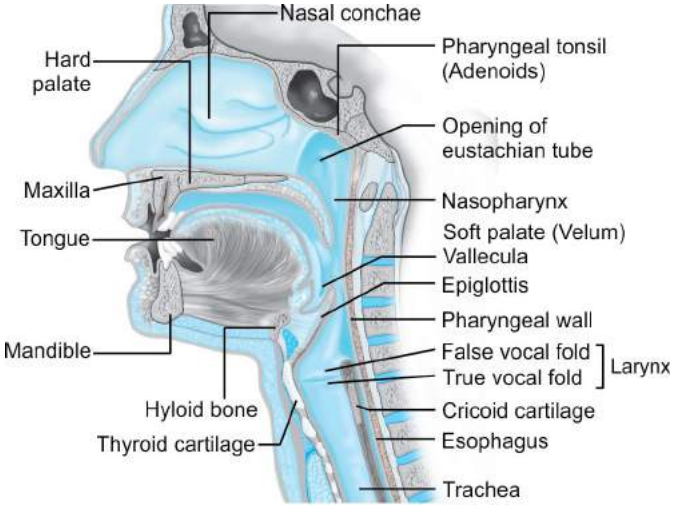
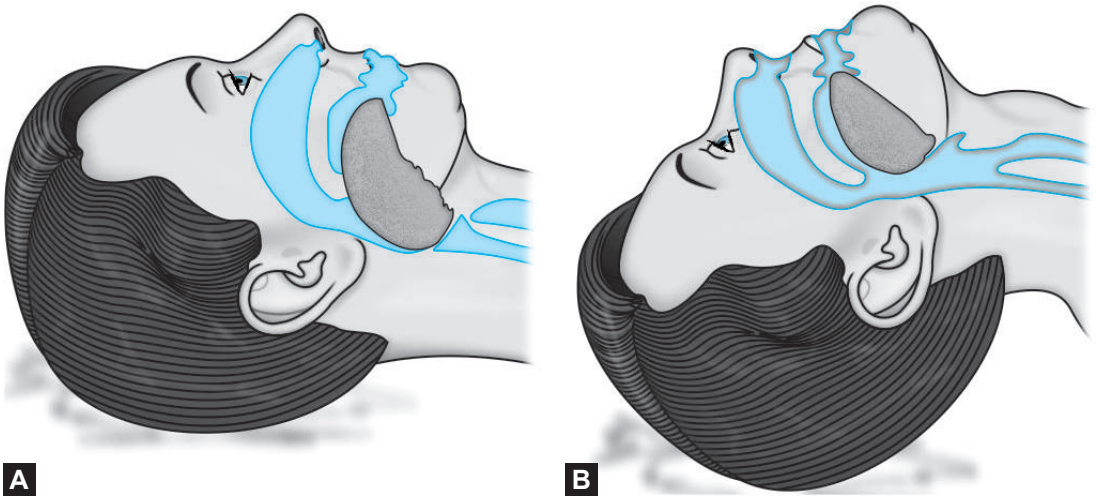


Fig. 2: Sagittal section—head and neck showing anatomy of the airway.

BASIC AIRWAY MANAGEMENT TECHNIQUES

- *Head-tilt chin-lift*: This is the simplest technique to ensure open airway in an unconscious patient, lifting the tongue away from posterior wall of pharynx (Figs. 3A and B). Palm of one hand applies pressure on patient's forehead to tilt the head back while first two fingers of opposite hand lift the chin (Fig. 4).



Figs. 3A and B: (A) Tongue obstructing the airway; (B) Head-tilt opens up the airway.

by mansdocs.com

- *Jaw-thrust maneuver (Figs. 5A and B)*: Jaw thrust is helpful in patient who may have cervical spine injury. In supine position, with index and middle fingers, the health care worker pushes the posterior aspect of mandible, while thumb pushes down the chin to open the mouth. The mandible displaces tongue forward with it and lifts it ensuring a patent airway.
- *Cervical spine immobilization*: It is used in suspected cervical spine trauma patients, to limit the movement of C-spine at time of airway management. Do not hyperextend the neck. In-line cervical immobilization should be applied by a second rescuer, who places himself/herself by the side of the patient, below the patient's shoulder level and stabilizes the jaw, neck and head. In this position, the rescuer providing cervical spine immobilization will not hinder the intubator's line of vision.



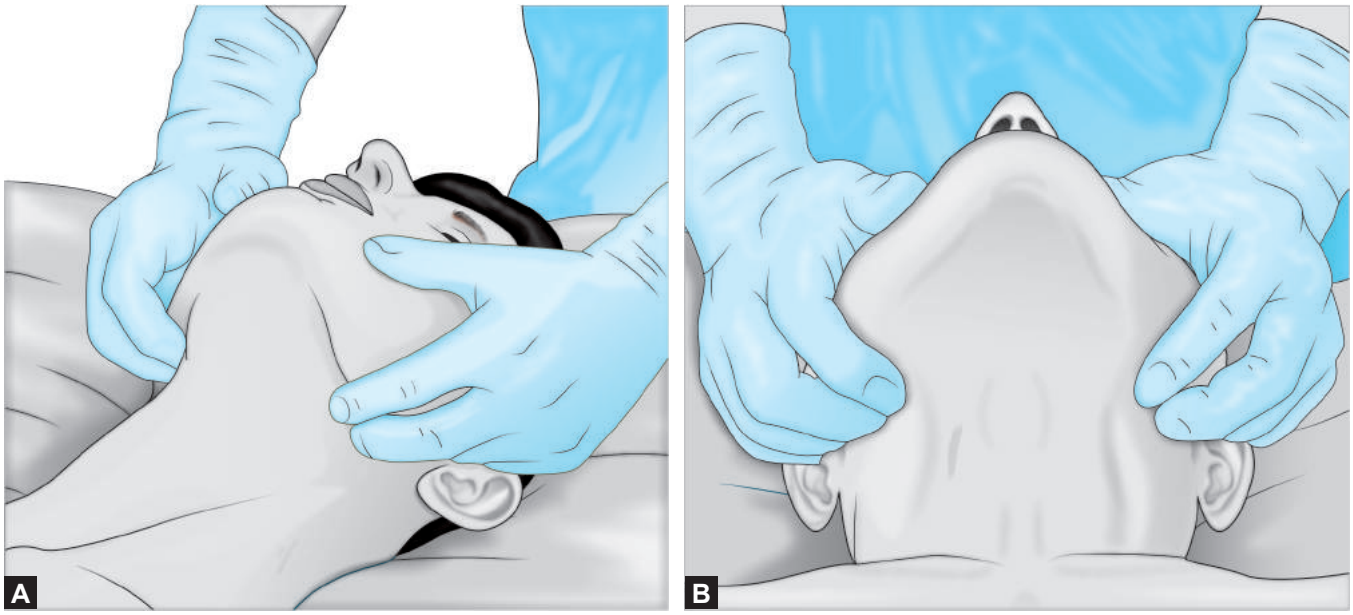
Fig. 4: Head-tilt and chin-lift procedures combined.

NONINVASIVE AIRWAY MANAGEMENT

Oropharyngeal Airways

These are J-shaped devices used to lift tongue and soft hypopharyngeal structures away from posterior wall of pharynx. These are available in different sizes along with color coding of bite portion as shown in the Figure 6.

Airways usually used are Guedel's airways which have a large flange (rests outside lips), a bite portion (lies between teeth) and tubular channel, pharyngeal end of which rests between posterior oropharynx and base of tongue.



Figs. 5A and B: (A) Bimanual elevation of lower jaw; (B) Bimanual elevation of lower jaw along with mouth opening.

by mansdocs.com

Insertion

It should be used only in unconscious or semiconscious patients to avoid coughing or laryngospasm. Size is estimated by placing airway next to patient's mouth and the pharyngeal tip lies next to angle of mandible (Fig. 7). The jaw is opened by left hand and airway is inserted with its concave side facing palate. Before the bite portion reaches the teeth, airway is rotated at 180° and slipped further in position. Alternatively, a tongue depressor is used to push down while airway is inserted with concave side down (Figs. 8A to D).

Uses

- To maintain patent airway in self-breathing semiconscious patients or during mask ventilation of semiconscious/unconscious patients.
- To prevent biting of ET or tongue or fiberscope or orogastric tube.
- To keep mouth open for suctioning.

Nasopharyngeal Airway

Nasopharyngeal airways are longer than oropharyngeal airway. It is passed through the nose and extends to just

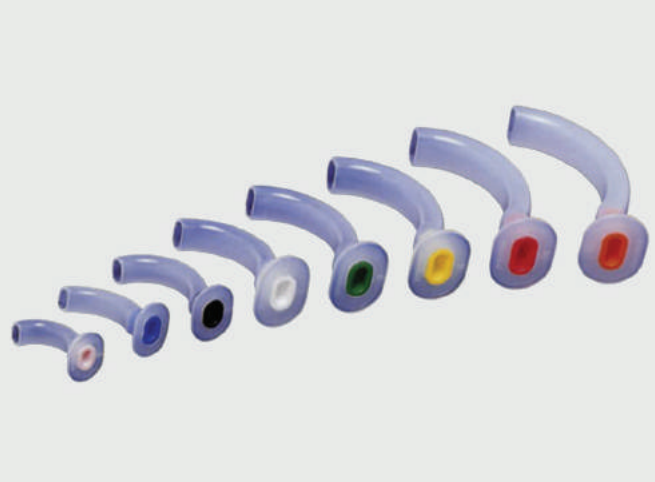


Fig. 6: Oropharyngeal airway.

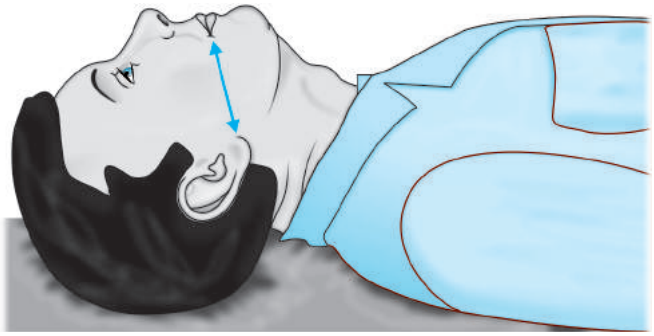
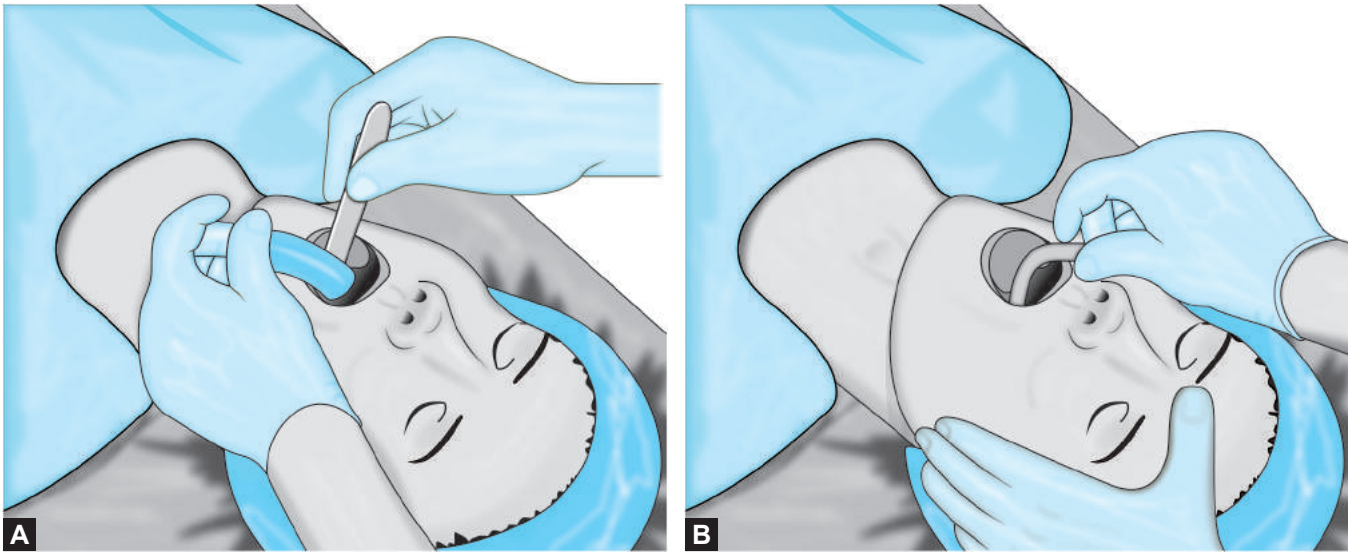
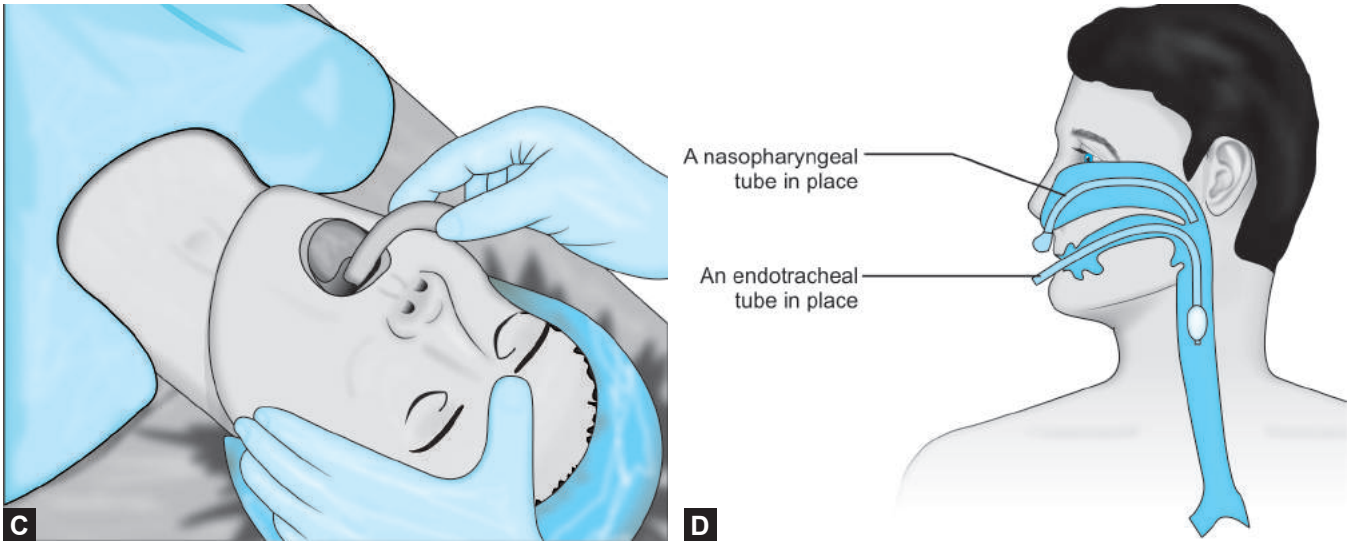


Fig. 7: Sizing the oropharyngeal airway.

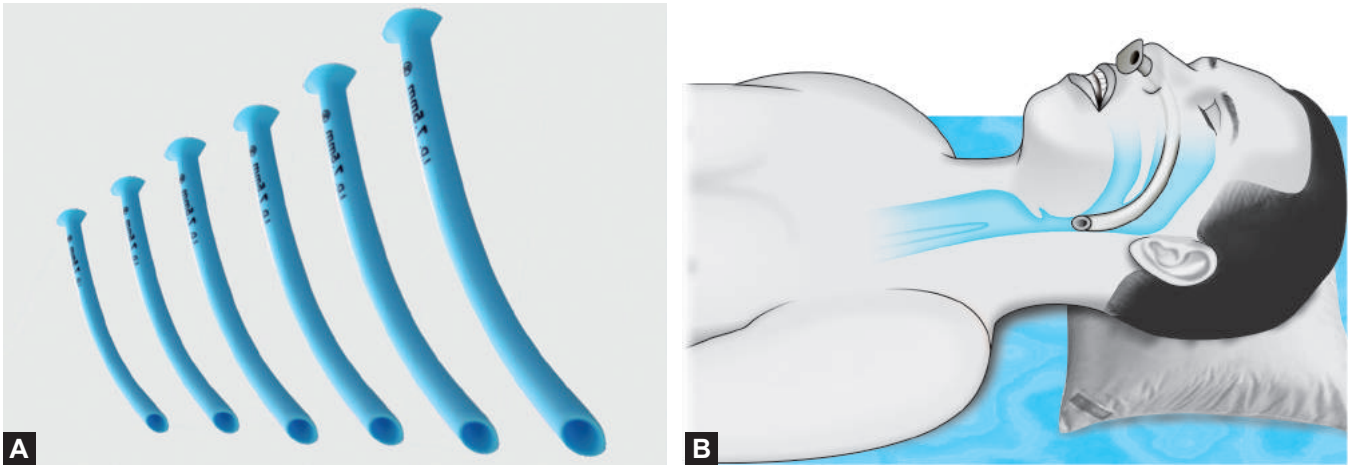


Figs. 8A and B: (A) Insertion of an oral airway using a tongue blade; (B) The airway may be placed "upside down".

by mansdocs.com



Figs. 8C and D: (C) Rotating the oropharngeal airway for the final placement; (D) Nasopharyngeal and orotracheal tube in place.



Figs. 9A and B: (A) Nasopharyngeal airway; (B) Nasopharyngeal airway in place.

above epiglottis. It is better tolerated than oropharyngeal airway by patients with intact airway reflexes (Figs. 9 A and B).

Indications

- Trauma/pathology of oral cavity
- When mouth cannot be opened
- Teeth are loose or in poor condition.

Contraindications

- Hemorrhagic disorder
- Anticoagulant therapy
- Skull base fracture
- Pathology, deformity of nose
- A history of nasal bleed requiring treatment.

Uses

- To facilitate suctioning
- Infants with Pierre Robin syndrome
- As a guide for fiberscope
- To treat hiccups
- To maintain patent airway during dental surgery.

Description

It has a flange and a slightly curved body (Figs. 9A and B). Diameters are same as for tracheal tubes. For adult male,

by mansdocs.com

7–7.5 mm and for female, 6.5–7 mm size is used. For insertion, airway is lubricated thoroughly, it is held perpendicularly in line with nasal passage with bevel facing against septum, and then it is inserted.

Complications

Airway obstruction: A incorrectly placed airway or one of small size may push tongue base against posterior pharyngeal and cover laryngeal aperture. Tip of airway can push epiglottis down over laryngeal opening causing blockade.

- Tongue edema/damage
- Trauma to nose, posterior pharynx, lip, tongue
- Dental damage
- Laryngospasm
- Ulceration and necrosis of soft tissue
- Retention, aspiration or swallowing of airway
- *CNS trauma*: In case of basilar skull fracture, trauma to anterior fossa may occur.

Bag and mask ventilation is an important skill that everyone must practice and learn. It may be difficult in certain situations like obesity, presence of a beard, edentulous patients, severely limited jaw protrusion, and snoring, a small thyromental distance (less than 6 cm) and trauma to the face or neck. Emergency care providers must also ensure airway cleared of vomitus or blood.

The self-inflating bag-valve mask system is the most commonly used system for emergency department and pre-hospital resuscitation. An appropriate mask is one that does not cover the patient's eyes and does not extend beyond the chin (Fig. 10). Typically, this mask is of anatomic design, with the pointed portion over the nose. The bag-valve mask unit should be attached to high-flow oxygen at 15 L/min. Place the patient in the "sniffing" or ear-to-sternal notch position, provided the patient does not require cervical spine immobilization. Additional maneuvers to assist with adequate positioning for BVM ventilation like head tilt-chin lift or jaw thrust can be used. The oropharyngeal and nasopharyngeal airways can be used as adjuncts if there is difficulty in ventilating.

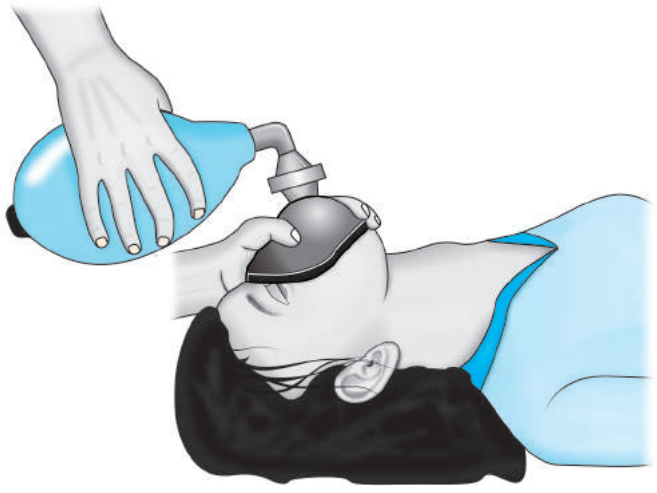


Fig. 10: Bag and mask ventilation

Traditionally, the "EC" hand position is utilized to obtain a seal with the mask. This position involves the thumb and index fingers holding the mask at the inferior and superior mask borders respectively. The other three fingers hold the mandible while performing the jaw thrust. If using the two-provider technique, one person should hold the mask with both hands, while the other provider bags the patient. The rate of ventilation for an adult is 10–12 breaths/min. Adequate chest rise should be seen.

Laryngeal Mask Airway

These are supraglottic devices used to secure airway by forming an inflatable circumferential seal over laryngeal inlet. They are used as a temporary airway management technique when bag–mask ventilation is difficult or in condition of failed endotracheal intubation.

Description

Laryngeal mask airway (LMA) consists of a shaft (i.e. a curved tube) attached to an elliptical cup-shaped mask at 30°. At the connection of mask with tube, there are two vertical bars to prevent obstruction of tube by epiglottis. The mask has an inflatable cuff, tube and a pilot balloon (Fig. 11). A black line runs longitudinally along the posterior aspect of tube which should be facing upper incisors after insertion. LMA is available in different sizes (Table 1).

Insertion Technique

Remove any visible obstruction or secretions from airway. Ensure IV access, pulse oximetry, electrocardiography (ECG) and blood pressure monitoring except in emergency situations.

Select appropriate size LMA and check cuff by inflating maximum allowable air into it. (which is 50% greater

by mansdocs.com

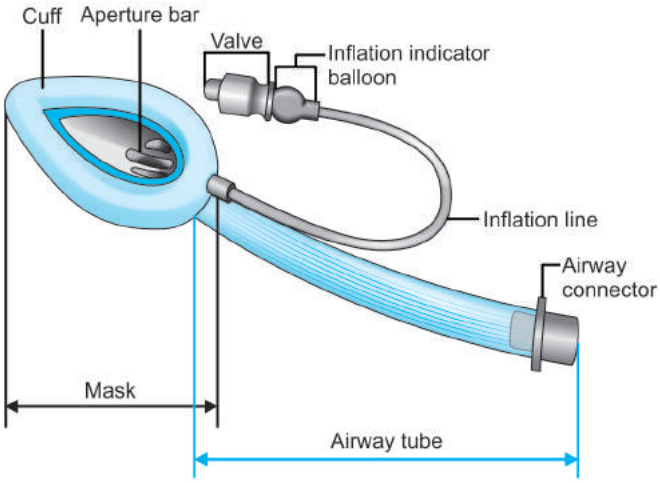


Fig. 11: Laryngeal mask airway.

Table 1: Selection of laryngeal mask airway (LMA) sizes.

LMA sizes	*Patient's weight (in kg)*	*Cuff inflation volume (mL)*	*Largest endotracheal intubation allowable (mm)*
1 5	5	3	
1.5	<10	8	3.5
2	10–20	12	4.5
2.5	20–30	20	5.5
3	30–50	20	6.0
4	50–70	30	6.5
5	>70	40	6.5

than recommended cuff volumes). Shape of cuff should be elliptical when inflated and there should be no kinking or abrasions on it.

The cuff should be then deflated to form a flat oval disk by pressing hollow side down against a clean flat surface. The deflated cuff should be wrinkle free.

The operator stands at head of the bed. Lubrication is applied on posterior surface of the cuff before insertion with a water soluble jelly. Patient is sedated to obtund airway reflexes, though not as deep as that required for endotracheal intubation. Adequacy of sedation can be judged by absence of motor response to jaw thrust.

The head should be extended and neck flexed (sniffing position). The left hand goes under head of patient and stabilizes occiput while right hand holds LMA (for right-handed persons) in a pen holding position and index finger presses at the point where tube joins the mask. With the concave surface of mask facing anteriorly and black line facing patient's upper lip, the LMA is inserted into mouth while pressing mask against hard palate to avoid folding of the deflated cuff (Figs. 12A to D).

Advance the LMA further down the oral cavity into hypopharynx by index finger maintaining backward pressure with slight pronation of forearm till definite resistance is felt. If not, withdraw index finger and push the shaft further down with left hand until resistance encountered.

Confirm correct positioning, by ensuring black line facing midline of upper lip. The cuff is inflated causing slight upward movement of entire LMA and a slight bulge at the front of the neck. Breathing system is connected and bilateral air entry is checked. Position is further confirmed by $ETCO_2$ monitoring. The tube is then secured by tape to maxilla.

Flexible LMA (Fig. 13)

It is a version of LMA with a flexible reinforced tube. It is available in five sizes; in each, the tube is longer and of smaller diameter than standard LMA. Being wire reinforced, it is more resistant to kinking while tube is positioned away from surgical field.

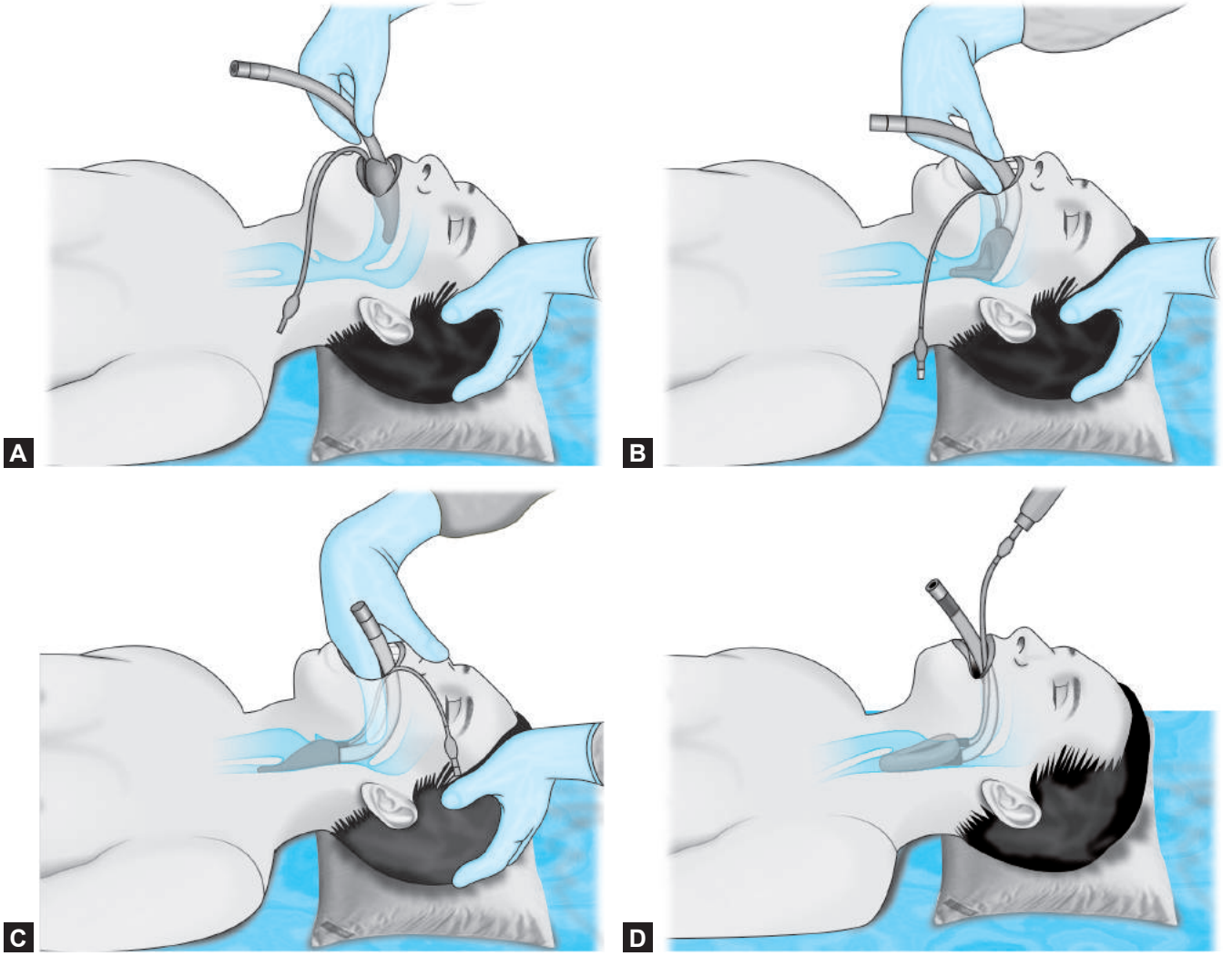
Intubating LMA (Fastrach™)

The tube of intubating LML (iLMA) is shorter and wider with a more acute curve and a metal handle attached to it (Fig. 14). There is a epiglottis elevating bar at the aperture to direct the endotracheal tube to the glottis. While inserting ensure the curved metal tube is towards chin. Rest technique is similar. A laryngoscope can be used to assist placement.

A well lubricated ET is passed down the iLMA through epiglottis elevating bar while gently lifting the iLMA with metal handle. Inflate ET cuff and conform placement. Position stabilizer rod on ET connector. Deflate iLMA cuff and remove it over ET-stabilizer assembly. Remove stabilizer rod, reconfirm ET placement and secure it with tapes.

LMA ProSeal (Fig. 15) is designed to provide additional benefits over the original LMA. It has a double tube arrangement, with a flexible wire reinforced airway tube and a drain tube. The drain tube opens at the upper esophageal sphincter and permits drainage of gastric secretions and is intended to prevent inadvertent gastric insufflation. The drain tube also protects the airway tube from occlusion by the epiglottis.

by mansdocs.com



Figs. 12A to D: (A) Insertion of laryngeal mask airway (LMA); (B) Insertion of LMA—sliding along the hard palate; (C) Insertion of LMA—finger guide for correct placement of LMA; (D) Final placement and cuff inflation.



Fig. 13: Flexometallic laryngeal mask airway.

by mansdocs.com

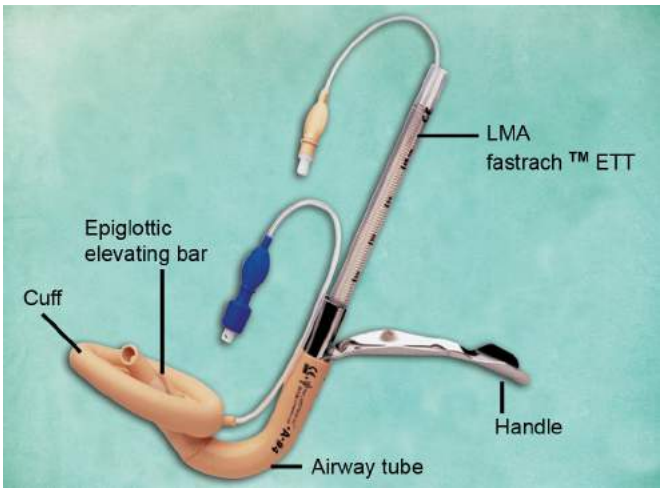


Fig. 14: Intubating LMA (iLMA).

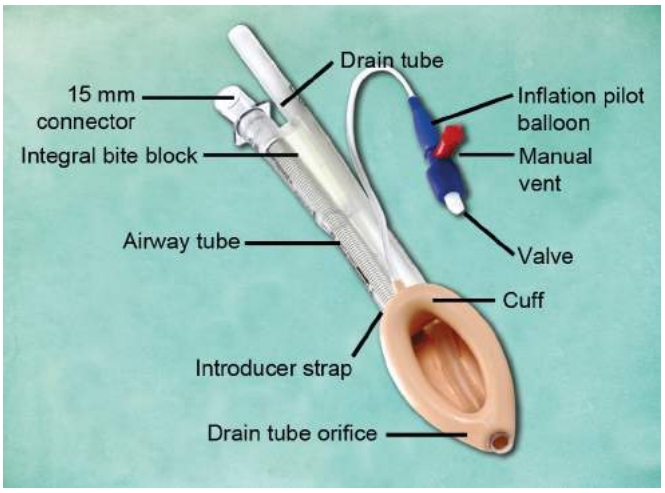


Fig. 15: ProSeal flexometallic LMA.

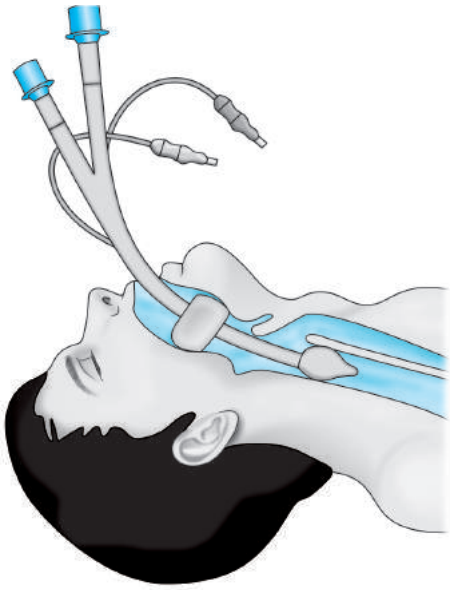


Fig. 16: Combitube.

The double cuff design (on adult sizes) enables good seal with minimal mucosal pressure.

A removable introducer tool is available to aid insertion. LMA ProSeal has a bite block to protect the airway tube.

Contraindication

- Inability to open mouth
- Pharyngeal pathology
- Obstruction at/below larynx
- Low lung compliance or high airway resistance.

Complications

- Aspiration
- Gastric distention
- Coughing/laryngospasm/bronchospasm
- Kinking/misplacement of LMA
- Partial airway obstruction.

INVASIVE AIRWAY MANAGEMENT

Esophageal-Tracheal Combitube (Fig. 16)

It is a double lumen tube used in emergency airway management. It has two lumens, one is esophageal tube that is blocked at distal end and has side openings and other is tracheal lumen which has a distal open end. It has two cuffs: a distal one and a proximal pharyngeal one. Usually, the tube enters esophagus and when both proximal and distal cuffs are inflated, patient is ventilated by side pharyngeal holes on esophageal tube. If not in esophagus, then breathing circuit is connected to tracheal tube and distal cuff is inflated. Barotrauma, esophageal rupture has been reported.

Endotracheal Intubation

This is most common definitive airway management technique used in ICU. Indications are respiratory failure needing ventilator support or high inspiratory concentration of oxygen and positive end-expiratory pressure (PEEP), acute upper airway obstruction, inability to clear secretions (low Glasgow coma scale), or at risk of aspiration (heavy post nasal bleed).

by mansdocs.com

Initial Assessment and Preparation

Prior to attempting intubation, availability of all relevant equipment should be checked. Difficult airway management facility should be assessable with in few minutes adequate preoxygenation (at least 3 minutes) is to be highly emphasized to with stand apnea during intubation. Critical patients may desaturate very fast during apnea periods due to under lying lung/heart pathology. High flow oxygen by mask and Ambu bag or Bain's circuit should be used. Head-tilt/chin-lift or jaw-thrust maneuver to mask ventilate the patients, and double handed technique may have to be used to ensure good chest rise while patients is being sedated.

A beard, heavy jaw, edentulous patient, facial injury/burns may make mask ventilation difficult.

The oropharyngeal secretions can be cleared by suctioning and airway patency can be achieved with oro/nasopharyngeal airway, if there is airway obstruction due to the tongue or pharyngeal soft tissue making mask ventilation difficult.

Call for help if difficult airway management is anticipated (discussed ahead). Cap, mask, and gloves are donned by ICU physician after good hand wash. Ventilator is set up, drugs to be used for sedation/anesthesia are kept ready at hand.

Direct Laryngoscopy

Cricoid pressure is usually required as ICU patients are usually not kept fasting for adequate time. Aspirate nasogastric tube, if in place. Position patient's head at waist of physician, flex the neck and extend head (morning air sniffing position) to align oral, pharyngeal and laryngeal axes with visual axis of the operator.

Selected drug therapy is given intravenously slowly. A combination therapy of fentanyl (0.05–0.4 mg/kg)/morphine (0.05–0.2 mg/kg) with midazolam (0.02–0.2 mg/kg) intravenously can be used. Other drugs like ketamine, thiopentone, propofol may be used. Preferred anesthetic agent is ketamine in hemodynamically unstable patients. Muscle relaxants may be used if adequate relaxation is not achieved by anesthetic/sedative drugs. Succinylcholine is ideal for rapid sequence intubation (RSI) but it is to be avoided in patients with hyperkalemia, severe acidosis, acute/chronic neuromuscular diseases, extensive burns and cervical trauma. ICU patients are at high risk for severe hypotension following use of sedatives. Therefore adequate hydration and availability of vasopressor with close monitoring of blood pressure during and after intubation is necessary.

During laryngoscopy, operator holds laryngoscope in left hand. Mouth is opened with right hand. Optimum size blade is inserted between teeth from right side and the tongue is swept toward left as the blade is advanced further into oral cavity. The tip of blade rests into the valleculla. With upward and forward motion of hand the epiglottis is lifted up, allowing the visualization of glottis opening. A well-lubricated ET is held in right hand and is passed through vocal cords under vision, cuff is inflated and bilateral air entry is checked by five point auscultation. Then tube is secured with tapes. Confirm tube placement further by $ETCO_2$ monitoring. Visualization of water vapors in the tube or chest rise may be less reliable. In case of difficulty BURP technique (backward, upward, rightward pressure) on larynx by an assistant may bring glottis into vision. A stylet can also be used with ET. In a difficult to visualize anterior larynx, a gum elastic bougie can be advanced into trachea in midline directed anteriorly and then ET can be guided over it. A hollow ET exchanger or a lighted stylet can also be used. If multiple attempts are to be made, restrict maximum interruptions in ventilation to about 30 seconds.

Complications

- Malplacement/endobronchial intubation leading to collapse of unventilated lung or barotrauma to ventilated lung. Esophageal intubation leading to hypoxia, bradycardia and cardiac arrest
- ET disconnection, displacement, blockage, kinking
- Hypertension, tachycardia, myocardial ischemia, raised intracranial pressure, raised intraocular pressure by laryngoscopy
- Severe hypotension by sedative or anesthetic drugs
- Airway trauma, bleeding in patients with coagulopathy.
- Aspiration pneumonitis
- Negative pressure pulmonary edema
- Sudden release of severe airway obstruction.

Cricothyroidotomy

Percutaneous or surgical, it is method of choice for severe airway obstruction in emergency. A horizontal incision is given in cricothyroid membrane. It is held wide open by a scalpel handle or forceps while a small tracheostomy or ET is inserted through it. Commercial cricothyroidotomy sets are also available using Seldinger technique. A tube of 3.0 mm will provide adequate ventilation with self-inflating bag connected to oxygen.

by mansdocs.com

Contraindications

Age less than 12 years.

Tracheostomy

Indications

- Glottis/supraglottic obstruction
- Tracheobronchial toilet
- A more comfortable airway in case of anticipated prolonged ventilation
- Protection against aspiration.

In uncomplicated patients, bedside percutaneous tracheostomy (PCT) performed by experienced ICU physician is more convenient, cost effective and as safe as surgical tracheostomy in OT. And also less infection rates have been suggested in PCT.

Contraindications

- Coagulopathy; international normalized ratio greater than 2; APC lesser than 40 × 107/L
- Significant anatomical abnormality in anterior neck
- tracheostomy scar
- Unstable cervical spine injury.

Techniques

Ciaglia's technique: A horizontal skin incision is made above or below the second tracheal ring, i.e. about two finger breadth above the vocal cords. A J-wire is inserted into trachea through needle at incision site. A series of curved dilators or a single modified tapered dilator is used to enlarge stoma. Tracheostomy tube is then inserted over guidewire and ET is removed.

Grigg's Technique: A Kelly's forceps is threaded over J wire to dilate the stoma prior to insertion of tympanostomy tube.

Complications

- Hemorrhage
- Surgical emphysema and pneumothorax
- Cricoid damage
- Infection of tracheostomy site
- Mucosal ulceration
- Tracheoesophageal fistula
- Tracheal stenosis
- Tracheomalacia.

DIFFICULT AIRWAY MANAGEMENT

Though 1–3% of patients in operating theatre are reported to have difficulty in managing airway, this percentage is significantly higher in ICU patients. Also the risk of rapid desaturation due to underlying lung or cardiac pathology is present. If a difficulty in managing airway is anticipated, call the senior most help available immediately. Failed repeated attempts may result in hypoxia or laryngeal trauma or edema, making successful airway control even more difficult.

Assessment of Difficult Airway

Following features help in predicting an airway problem, a combination of which is more reliable rather than individual factors. Muscle relaxation should be strictly avoided if there is a suspicion of difficulty in airway.

Anatomical Features

- Short neck or thyromental distance less than 6 cm (three finger)
- Limited neck mobility, i.e. inability to touch chest with chin or extend neck
- Long upper incisors, small mouth, long high curved palate, receding mandible
- Limited mouth opening, i.e. inter incisor distance less than 3 cm (two finger)
- Space occupying lesion or trauma of face/oropharynx/larynx.

Mallampati Classification

- Though to be examined in a sitting patient with mouth wide open eyes of examiner at level of mouth of patient, it is not a ideal position for ICU patient. Class more than 2 predicts difficulty in intubation (Fig. 17).

Cormack–Lehane Classification

It is based on examination of laryngeal structures on direct laryngoscopy. More than grade 2 predicts difficulty in intubation.

Grade 1: Complete glottis visible.

Grade 2: Anterior glottis not visible.

Grade 3: Only epiglottis visible: (a) mobile, (b) not mobile

Grade 4: Epiglottis not visible.

The techniques used in difficult intubation and difficult ventilation are listed in Table 2.

by mansdocs.com

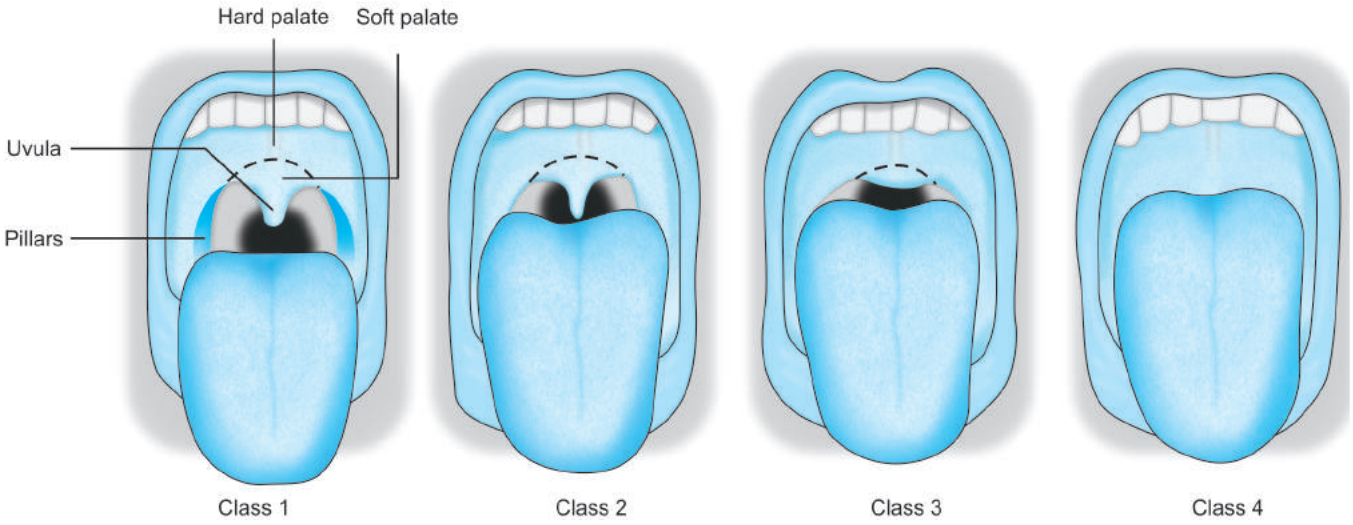


Fig. 17: The mallampati score: Class 1. Complete visualization of the soft palate; Class 2. Complete visualization of the uvula; Class 3. Visualization of only the base of the uvula; Class 4. Soft palate is not visible at all

Table 2: Techniques for difficult airway management.

Techniques for difficult intubation	*Techniques for difficult ventilation*
• Alternative laryngoscope blades	• Esophageal tracheal Combitube
• Awake intubation	• Intratracheal jet stylet
• Blind intubation (oral or nasal)	• Laryngeal mask airway
• Fiberoptic intubation	• Oral and nasopharyngeal airways
• Intubating stylet or tube changer	• Rigid ventilating bronchoscope
• Laryngeal mask airway as an intubating conduit	• Invasive airway access
• Light wand	• Transtracheal jet ventilation
• Retrograde intubation	• Two-person mask ventilation
• Invasive airway access	

Table 3: Suggested contents of the portable storage unit for difficult airway management.

1. Rigid laryngoscope blades of alternate design and size from those routinely used; this may include a rigid fiberoptic laryngoscope
2. Tracheal tubes of assorted sizes
3. Tracheal tube guides. Examples include (but are not limited to) semirigid stylets, ventilating tube changer, light wands, and forceps designed to manipulate the distal portion of the tracheal tube
4. Laryngeal mask airways of assorted sizes; this may include the intubating laryngeal mask airway and the *LMA-ProSeal*™ (LMA North America, Inc., San Diego, CA)
5. Flexible fiberoptic intubation equipment
6. Retrograde intubation equipment
7. At least one device suitable for emergency noninvasive airway ventilation. Examples include (but are not limited to) an esophageal tracheal Combitube (Kendall-Sheridan Catheter Corp., Argyle, NY), a hollow jet ventilation stylet, and a transtracheal jet ventilator
8. Equipment suitable for emergency invasive airway access (e.g. circothyrotomy)
9. An exhaled CO_2 detector

The items listed in this table represent suggestions. The contents of the portable storage unit should be customized to meet the specific needs, preferences, and skills of the practitioner and healthcare facility.

The American Society of Anesthesiologists algorithm for difficult airway is described in the Flowchart 1. The equipment required in the difficult airway cart is listed in Table 3.

by mansdocs.com

Flowchart 1: Difficult airway management.

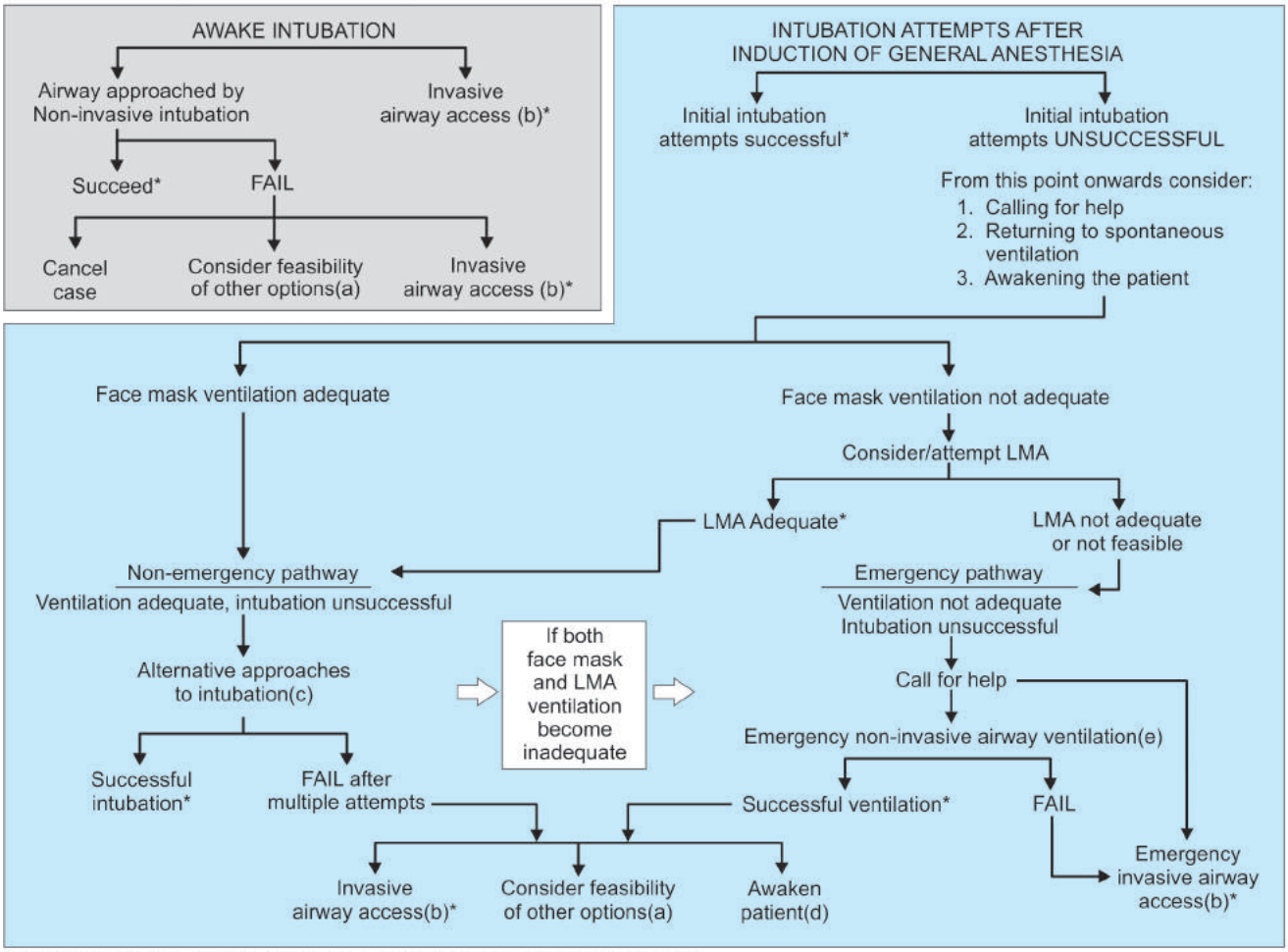
AMERICAN SOCIETY OF ANESTHESIOLOGISTS

DIFFICULT AIRWAY ALGORITHM

1. Assess the likelihood and clinical impact of basic management problems:
   - A. Difficult ventilation
   - B. Difficult intubation
   - C. Difficulty with patient cooperation or consent
   - D. Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management
3. Consider the relative merits and feasibility of basic management choices:

A.	Awake intubation	vs.	Intubation attempts after induction of general anesthesia
B.	Non-invasive technique for initial approach to intubation	vs.	Invasive technique for initial approach to intubation
C.	Preservation of spontaneous ventilation	vs.	Ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



*Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2

a. Other options include (but are not limited to): surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the emergency pathway.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Options for emergency non-invasive airway ventilation include (but are not limited to): rigid bronchoscope, esophageal-tracheal combitube ventilation, or transtracheal jet ventilation.

by mansdocs.com

BIBLIOGRAPHY

1. American Society for Testing and Materials. Standard specification for anesthetic equipment-oropharyngeal and nasopharyngeal airways (F 1573-95). West Conshohocken PA: ASTM, 1995.
2. Biodin MP, Airway patency in unconscious patient. Br J Anesthesia. 1985;57:306-1.
3. Brain AIJ, Verghese C. The Intubating Laryngeal Mask (FasTrach) Instruction Manual. San Deigo, CA: LMA North America; 1998.
4. Brain AIJ. The laryngeal mask: a new concept in airway management. Br J Anesthesia. 1983;55:801-4.
5. Brimacombe J,Berry A, Verghese C. The laryngeal mask airway:its uses in anesthesiology. Anesthesiology. 1994; 80:706-7.
6. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy. Chest. 1985;87:715-9.
7. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. Anaesthesia. 1984;39:1105-11.
8. Delany A, Bagshaw SM, Nalos M. Percutaneous dialatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. Crit Care. 2006;10:R55.
9. Frass M, Frenzer R, Rauscha F, et al. Evaluation of esophageal tracheal combitube cardiopulmonary resuscitation. Crit Care Med. 1986;15:609-11.
10. Griggs WM, Worthley LIG, Gilligan JE, et al. A simple percutaneous tracheostomy technique. Surg Gynaecol Obstet. 1990;170:543-5.
11. Konrad C, Schupfer G, Witlisbach M, et al. Learning manual skills in anesthesiology: is there a recommended number of cases for anesthetic procedures? Anesth Analg. 1998;86: 635-9.
12. Kress TD, Balasubramaniam S. Cricothyroidotomy. Ann Emergency Medicine. 1982;11:197-201.
13. Mallampati SR, Gugino LD, Desai SP et al. A clinical sign to predict difficult tracheal intubation: a prospective study. Can J Anaesth. 1985;32:429-34.
14. Marsh AM, Nunn JF, Taylor SJ, et al. Airway obstruction associated with use of the Guedel airway. Br J Anesthesia. 1991;67:517-23.
15. McGee JP, Vender JS. Nonintubation management of the airway. In clinical procedures in anesthesia and intensive care. JL Benumofed.,Philadelphia, PA: JB Lippincott Co; 1992. pp 89-114.
16. Pryor JP, Reilly PM, Schapiro MB. Surgical airway management in ICU. Crit Care Clin. 2000;16:473-88.
17. Silvester W, Goldsmith D, Uchino S, et al. Percutaneous versus surgical tracheostomy; a randomized controlled study with long-term follow-up. Crit Care Med. 2006;34: 2145-52.
18. Stoneham MD. The nasopharyngeal airway. Assessment of position by fiberoptic laryngoscopy. Anesthesia. 1993; 48:575-80.
19. The American Heart Association in Collaboration with the International Liaison Committee on Resuscitation (ILCOR): Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 200;102:1.

by mansdocs.com

CHAPTER

3

Hemodynamic Monitoring in ICU

Vijaya P Patil, Nayana Amin, Vandana Agarwal

INTRODUCTION

Majority of the patients in any intensive care unit (ICU) are either admitted with hemodynamic instability or become hemodynamically unstable during the course in ICU. The consequence of the organ hypoperfusion will vary from patient to patient, depending on the degree and duration of hypoperfusion, the number of organ systems affected, and the presence of prior organ dysfunction. The challenge to the intensivist is to identify the hypoperfusive state and rapidly restore the cellular perfusion to avoid organ dysfunction and failure. Hemodynamic monitoring is used for early identification of hypoperfusivestate, to identify its probable cause and rapidly restore cellular perfusion. Some form of monitoring is also used to detect early signs in patients who are at risk of developing hemodynamic compromise and initiate appropriate therapy.

Hemodynamic monitoring can be invasive or noninvasive, or continuous or intermittent. Monitoring devices can measure physiologic variables directly or derive these variables through signal processing. One can also classify hemodynamic monitoring as monitoring of upstream parameters, monitoring of downstream parameters and monitoring of microcirculation.

PHYSIOLOGICAL CONSIDERATIONS

The purpose of hemodynamic monitoring in critically ill patients is to assess tissue oxygenation, establish the diagnosis and to guide therapeutic interventions to optimize oxygen balance. The two components of oxygen balance are oxygen delivery (DO_2) and oxygen consumption (VO_2). Oxygen delivery is the amount of oxygen which is delivered to the tissues and it is this component of oxygen balance which can be altered significantly by clinical interventions. The determinants of DO_2 are cardiac output (CO) and arterial oxygen content (CaO_2) of blood. The arterial oxygen content of blood is the amount of oxygen bound to hemoglobin and the amount of dissolved oxygen. It can be calculated by the formula:

$$CaO_2 = (Hb\ g/dL \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

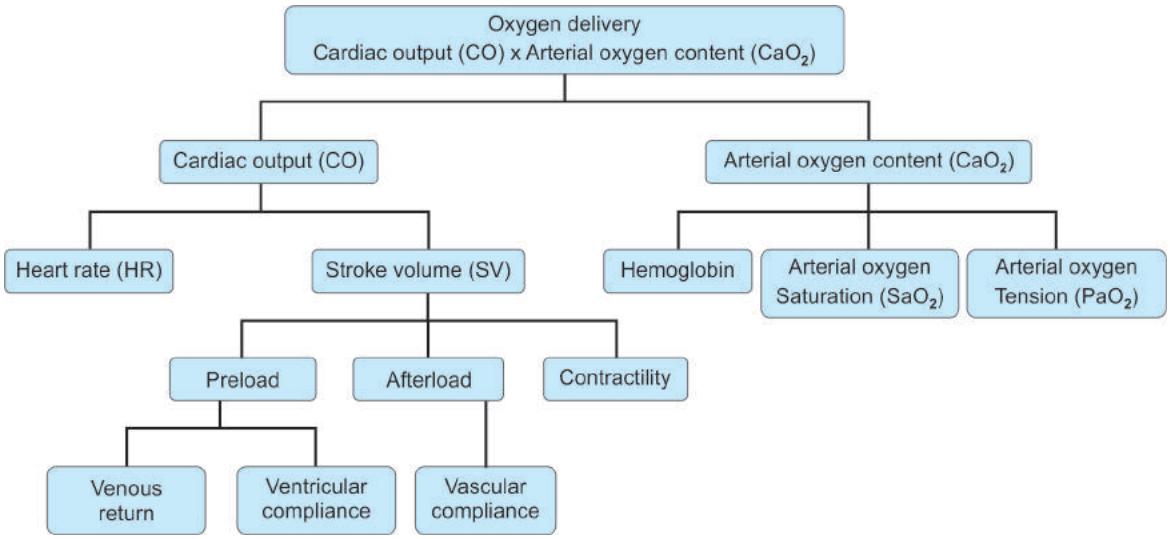
Where, SaO_2 is the arterial oxyhemoglobin saturation and PaO_2 is the partial pressure of oxygen in the arterial blood.

The arterial oxygen content represents the amount of oxygen in the arterial circulation but it does not give any information about the amount of oxygen that is delivered or consumed by the tissues. Even if CaO_2 is normal, a good CO is required to deliver oxygen to the tissues. CO is the product of heart rate (HR) and stroke volume (SV). Increase in HR is the first compensatory mechanism of increasing CO or DO_2. Even if CO cannot be measured, an indirect assessment of the variables involved in determining the CO and the knowledge of the hemodynamic principles can help in monitoring critically ill patients (Flowchart 1).

To effectively interpret the hemodynamic parameters, it is important to understand the cardiovascular physiology and blood homeostasis. Generally, whenever there is decrease in CO, it will also result in a decrease in the mean arterial pressure (MAP). This will stimulate the baroreceptors in the aortic arch and carotid body to activate the

by mansdocs.com

Flowchart 1: Determinants of oxygen delivery.



sympathetic nervous system. This response would try to restore MAP by increasing HR and increase in the vasomotor tone. Thus, a normal blood pressure does not always indicate hemodynamic stability and if there is persistent hypotension, it indicates that there is failure of cardiovascular system to compensate for circulatory shock. Also whenever there is increased oxygen demand, body tries to meet it by increasing CO.

The cardiac output will be decreased in cardiogenic, hypovolemic and obstructive shock and increased in early distributive shock. However, in all types of shock, generally there will be tachycardia due to sympathetic activation.

In cardiogenic shock, there is primary cardiac failure either due to impaired contractility (myocardial ischemia/infarction, electrolyte imbalance, hypoxemia, hypothermia, endocrinologic diseases, metabolic poisoning, etc.), or poor diastolic compliance (fibrosis, infiltrative cardiomyopathies, hypertrophy). It can also be due to ineffective SV as seen in dysrhythmias (impaired filling), ventriculoseptal defect (abnormal flow through alternate paths) or valvulopathy. In left heart failure, there will be increased cardiac filling pressures [right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP)] and pulmonary edema. In right heart failure, there will be increase in RAP but PAOP may be low or normal.

In hypovolemic shock, there is decrease in effective circulating blood volume and venous return either due to hemorrhage, capillary leak, diarrhea, vomiting and insensible loss through skin with burns or due to an increase in unstressed vascular volume (loss of sympathetic tone, spinal cord injury, vasodilating drugs). Thus, in hypovolemic shock, there will be decreased filling pressures.

In obstructive shock, there is blockage to the flow of blood either due to right ventricular (RV) outflow obstruction [pulmonary embolism, auto-positive end-expiratory pressure (auto-PEEP)], tamponade (pericardial effusion, tension pneumothorax), or left ventricular (LV) outflow obstruction (aortic stenosis, dissecting aortic aneurysm). The findings of obstructive shock will depend on underlying pathology. In cases like pulmonary embolism or aortic dissection where there is increased ventricular afterload, filling pressures (RAP or PAOP) would be high. But in cases like cardiac temponade or tension pneumothorax, there would be decreased ventricular preload.

There is loss of vasomotor tone in distributive shock (sepsis, spinal shock, vasodilating drugs, and metabolic poisons). In early stages of distributive shock, there will be increased CO, DO_2, and mixed venous oxygen saturation (SvO_2) whereas in late stages, there will be decreased CO. Thus, one can diagnose underlying pathology by looking at various parameters.

HEMODYNAMIC MONITORING: CLINICAL

Clinical assessment of organ functions can help to identify adequacy of regional perfusion in early stages of shock. Changes in higher cortical functions, cardiorespiratory system and kidneys can lead the clinician to identify hemodynamic compromise.

by mansdocs.com

Altered mentation in the form of drowsiness or agitation suggests cerebral hypoxia, main etiology being cerebral hypoperfusion. In the absence of flow limiting lesions in main arteries or raised intracranial pressure (ICP), hypoperfusion is due to arterial hypotension.

In circulatory failure, blood flow is diverted from the less important tissues (skin, subcutaneous, muscle, gastrointestinal tract) to vital organs (heart and brain). Thus, monitoring perfusion in these less vital tissues could be an early marker of hypoperfusive state (compensated shock). The cutaneous circulation is deprived of autoregulation, and the sympathetic neurohumoral response predominates, resulting in decreased skin perfusion and temperature in low flow conditions. Clinical signs of poor peripheral perfusion consist of a cold, clammy, and mottled skin, associated with an increase in capillary refill time (CRT). Prolonged CRT in pediatric patients has been found to be a good predictor of dehydration, reduced SV, and increased blood lactate levels; however, in adults, it has been shown to be unreliable.

Temperature gradients: The heat conduction to the skin by the blood is also controlled by the degree of vasoconstriction. Under stable hemodynamic conditions, heat is conducted from the core to the skin, whereas reduction in blood flow decreases the heat conduction from the core to skin. During vasoconstriction, the temperature of the skin falls due to decreased heat conduction from the core, and therefore, the core temperature rises and the gradient between cores to periphery increases. In stable patients, there exists a gradient of 3–7°C which increases in states of reduced CO.

Patients in shock are often *tachycardic*. If the HR decreases in response to a fluid challenge then it indicates hypovolemia. The HR more than 130 beats/min in adults results in decrease in diastolic filling time which itself can lead to a decrease in CO by decreasing the SV due to a decrease in preload. Depressed coronary perfusion as a consequence of systemic arterial hypotension and increased myocardial oxygen demand due to tachycardia can worsen cardiac function further leading to perpetuation of shock. Myocardial hypoxia can also lead to cardiac dysrhythmias and further impair cardiac function.

Tachypnea is one of the first signs that reflect reduced blood flow and oxygen transport. The cardiovascular and respiratory systems work together. If blood flow around the body is compromised in any way, DO_2 to tissues is reduced. To compensate for this, ventilation is increased to attempt to increase oxygen uptake in the lungs.

Pulse oximetry and peripheral perfusion index: The principle of the pulse oximetry is the difference in absorbance of light with different wavelengths (660 nm and 940 nm) by oxygenated hemoglobin. Other tissues, such as connective tissue, bone and venous blood, also absorb light and thus affect the resulting signal. So, to have a proper estimate of the arterial oxygen saturation of the hemoglobin, the pulse oximetry has to distinguish the pulsatile component from the nonpulsatile component. In circulatory failure due to hypovolemia and low CO, there is increased vasoconstriction and resultant decreased perfusion of the skin. The perfusion index, displayed in many new monitors, is calculated as the ratio between the pulsatile and the nonpulsatile component of the light reaching the detector of the pulse oximetry. When peripheral hypoperfusion exists, the pulsatile component decreases, and because the nonpulsatile component does not change, the ratio decreases. Studies have suggested a ratio of 1.4 as cutoff that reflects poor peripheral perfusion in critically ill patients.

Low blood pressure is often seen in patients with shock but it does not indicate underlying pathology. Noninvasive blood pressure measurement techniques actually measure flow; hence, this technique is unreliable in the presence of vasoconstriction and low flow states. It is also unreliable in the presence of extreme tachycardia, arrhythmias, shivering or improper cuff size. These techniques underestimate the blood pressure in low flow states and overestimate the blood pressure in high flow states. Inappropriate cuff size can give inaccurate blood pressure readings (too small cuff overestimates the BP, and too large cuff underestimates BP).

Low urine output is one of the earliest signs of inadequate tissue perfusion. Urine output may be decreased even before there are any changes in the HR or blood pressure. Oliguria in the patient without prior renal insufficiency can be a valuable indirect indicator of shock that mandates close observation of urinary output in patients who are at risk for hypoperfusion. Resuscitation of patients in shock can be guided by response of urine output, provided there are no confounding factors (diabetic ketoacidosis, diabetes insipidus, diuretic therapy, etc.)

Advantage of noninvasive monitoring is that it does not need costly gadgets and can be performed even in ward. However, they are subjective and not very specific, and should be used for initial evaluation. Once the clinical signs and noninvasive monitoring suggests that patient is in shock, additional monitoring will be required to assess the adequacy of CO and oxygen balance and to guide further therapy.

by mansdocs.com

MONITORING INVASIVE ARTERIAL BLOOD PRESSURE

Direct arterial blood pressure (ABP) monitoring is the only scientifically and clinically validated method that allows real time and continuous monitoring of a patient's ABP carrying information about the dynamics of arterial pressure during the cardiac cycle.

Arterial lines are most commonly inserted in the radial, femoral or dorsalis pedis. Femoral site is associated with increased risk of infectious complications and should be chosen only in case where peripheral pulses are not well felt. Prior to insertion of the arterial line, it is important to perform the Allen's test to document good collateral circulation to minimize the risk of ischemic complications. Once the arterial catheter has been inserted, it should be connected to a pressure transducer. The transducer should be primed with saline to remove all the air bubbles and zeroed to atmospheric pressure. It should then be leveled to the phlebostatic axis (vertical dropped from the 4th intercostal space bisecting a horizontal line passing through the midpoint of anteroposterior diameter of the chest) (Fig. 1). Leveling is important because every 10 cm increase or decrease in the position of the transducer will decrease or increase the measured pressure by 7.4 mm Hg respectively.

The mean arterial pressure (MAP) is the driving pressure for perfusion of most of the vital organs. If the MAP falls below the limit of autoregulation, the regional circulation will proportionately decrease with decrease in MAP. The target MAP would vary for different organs and will depend on various factors like age, history of hypertension, vasoactive therapy and neurovegetative state. The target MAP in the presence of uncontrolled bleeding should be 40 mm Hg until the bleeding is controlled. In patients with traumatic brain injury without any evidence of systemic bleeding, MAP should be 90 mm Hg and in all other shock states, the MAP should be above 65 mm Hg. Studies have shown that in septic patients increasing MAP to 85 mm Hg does not improve tissue oxygenation or regional perfusion. However, hypertensive patients will need higher perfusion pressures as compared to normotensive patients due to high autoregulatory level.

Lots of information can be gathered from shape of arterial waveform as well. The slope of the upstroke of the arterial pressure waveform reflects myocardial contractility (dp/dt). The stroke volume can be calculated by measuring the area from the beginning of the upstroke to the diacritic notch (Fig. 2).

For proper interpretation of ABP, it is important that system is optimally functioning. An underdamped waveform shows a high systolic and low diastolic pressure, and it can result from factors like long-tubing or patient factors like vasoconstriction, hypertension, atherosclerosis, aortic regurgitation, etc. An overdamped waveform shows low systolic and high diastolic pressure and can result from factors like presence of air bubbles in the tubing, very compliant tubing, presence of blood clots/fibrin, catheter kinks, low pressure in the flush bag/no fluid in flush bag, and presence of stopcocks or injection ports (Fig. 3). Patient factors like aortic stenosis, vasodilatation and low CO states like cardiogenic shock, sepsis or severe hypovolemia can result in overdamped waveforms. Equipment factors can be ruled out by performing the dynamic response testing (fast flush test).

Pulse pressure depends on SV and arterial stiffness. Normal pulse pressure is 30–40 mm Hg. Wide pulse pressure can be seen in conditions like vasodilatation, anemia,

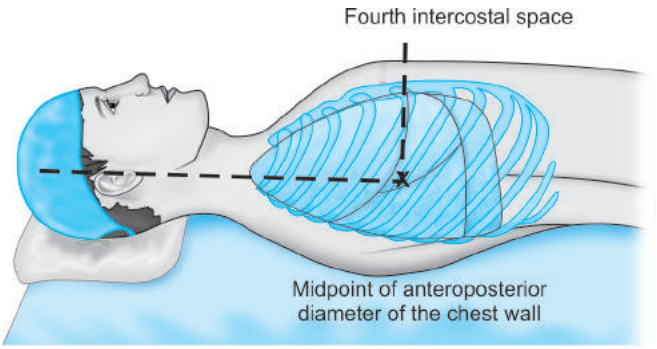


Fig. 1: Phlebostatic axis.

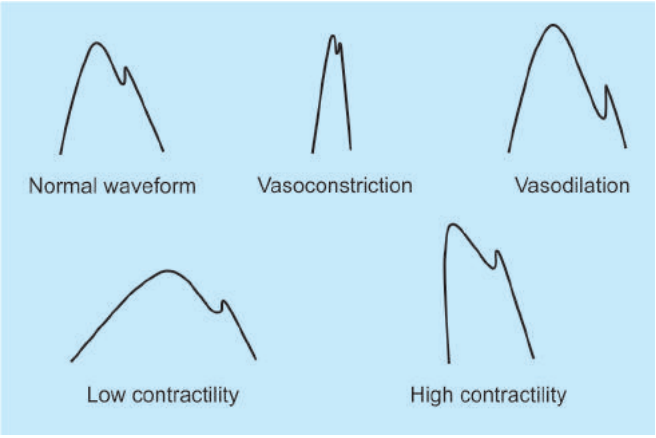


Fig. 2: Variations in arterial waveform.

by mansdocs.com

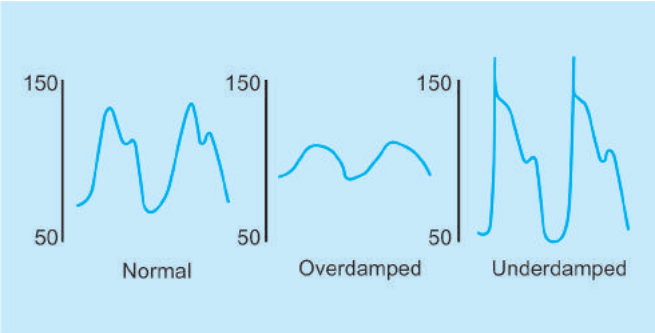


Fig. 3: Arterial waveform.

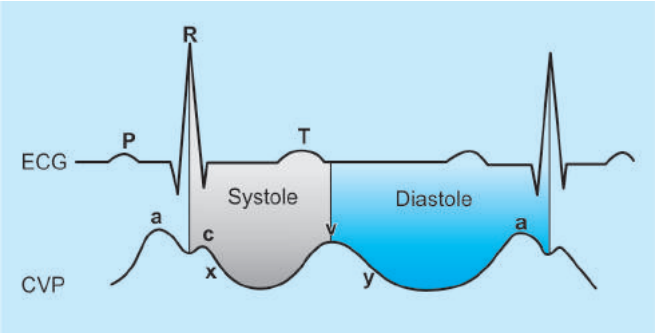


Fig. 4: Central venous pressure (VP) waveform.
(CVP: Central venous pressure; ECG: Electrocardiograph).

pregnancy, aortic regurgitation, thyrotoxicosis, atherosclerosis, hypertension, raised ICP, etc. Narrow pulse pressure is seen in hypovolemia, aortic stenosis, cardiac tamponade, etc. A patient who has wide pulse pressure with low diastolic pressure is likely to need vasopressor therapy, whereas a patient with narrow pulse pressure is likely to need fluid therapy and/or isotropic support.

Central Venous Pressure

Preload is one of the determinants of CO. It is the amount of blood remaining in the heart at the end of diastole. The distensibility of the ventricle and the volume load that it can accept is the basis of the frank starling curve. Greater the end diastolic volume (preload), greater is the stretch on the myocardial fibers and better is the SV. Clinicians try to estimate the volume (end-diastolic volume) status from pressure (end-diastolic pressure) which is transmitted and reflected as atrial pressures. Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are most commonly used measurements to measure right and LV preloads respectively.

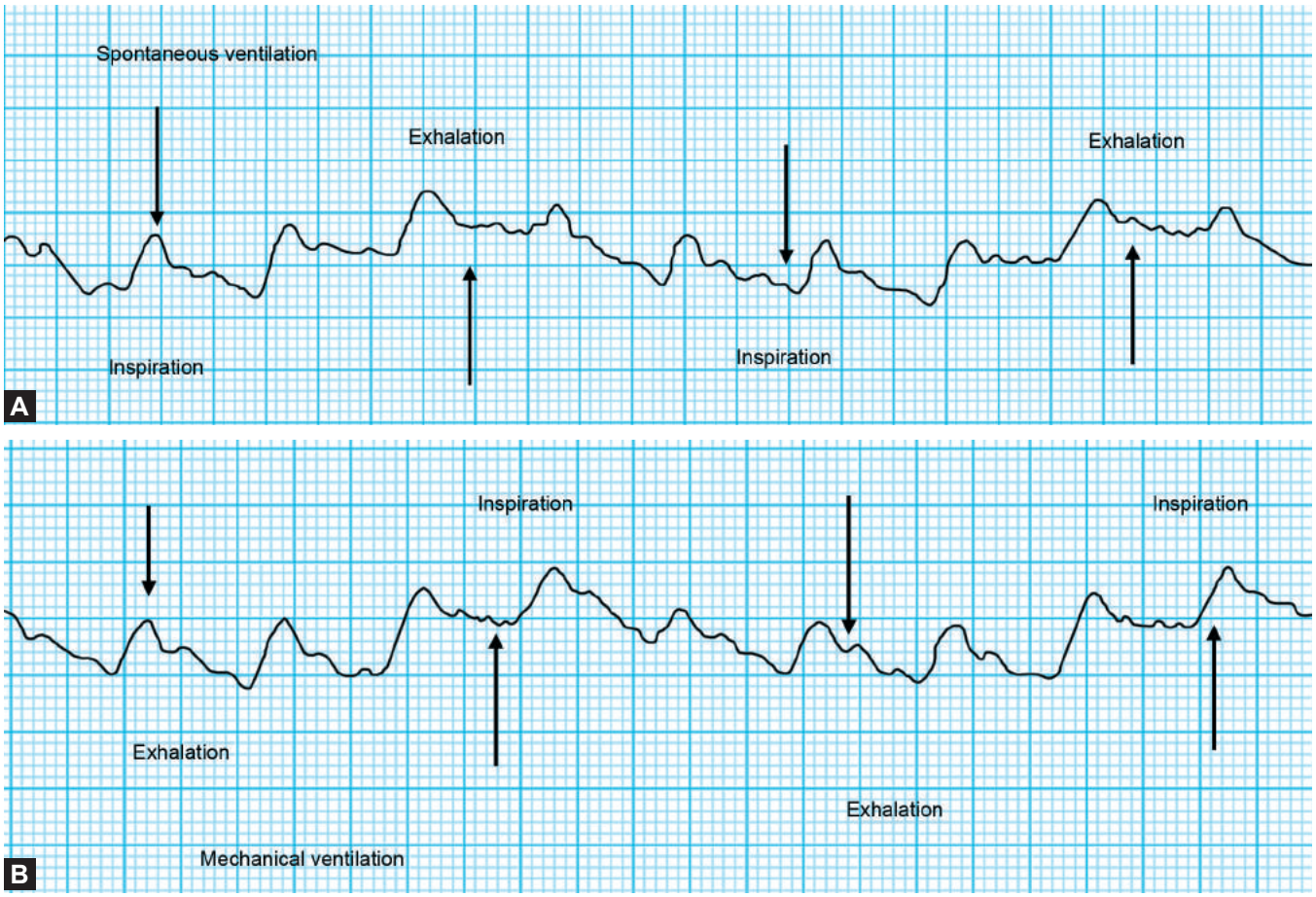
Central venous pressure can be estimated from lines put in the internal jugular or subclavian veins. Radiologically, the ideal position for the tip of central venous catheter placed in the upper body is 1 cm above the carina [near superior vena cava (SVC) and right atrium (RA) junction]. A CVP trace has three positive deflections (a, c and v) and two negative deflections (x and y). "a" wave is caused by atrial contraction and follows the P wave on ECG. This is followed by atrial relaxation resulting in a decrease in pressure after the "a" wave. The "c" wave is due to isovolemic contraction of right ventricle causing the tricuspid valve to bow back into the RA. It follows the QRS on ECG. During atrial relaxation, the atrial pressure continues to decrease resulting in "x" descent. "v" wave is due to an increase in the atrial pressures due to filling of the atrium with blood from the vena cava. It is seen just after the T wave on ECG. As the tricuspid valve opens, the blood flows from atrium to the ventricle producing the "y" descent as a result of decrease in atrial pressure (Fig. 4).

In atrial fibrillation, the "a" wave disappears and the "c" wave becomes more prominent. Cannon "a" waves are seen in junction rhythm, mitral or tricuspid stenosis, atrioventricular dissociation and ventricular pacing. Large "v" waves are seen in tricuspid valve regurgitation, hypovolemia and ventricular failure.

Peak of the "a" wave coincides with the point of maximal filling of right ventricle, while the base of "c" wave is the last atrial pressure before the ventricular contraction and is therefore the best estimate of cardiac preload. Hence, CVP should be measured at the base of "c" wave. If "c" wave cannot be identified then the measurements can be taken at the base of "a" wave. The atmospheric pressure is used as a reference point for measuring CVP. The pleural and pericardial pressures almost equal the atmospheric pressure at the end of expiration. This is true for both spontaneous and controlled ventilation. CVP should always be measured at end-expiration as it provides the best estimate for the transmural pressure and cardiac preload (Figs. 5A and B).

Central venous pressure reflects a balance between blood volume, cardiac function and venous capacitance. It is also influenced by the intrathoracic pressures. CVP can be decreased due to hypovolemia and venodilation. In the presence of hyperdynamic heart, the CVP can be low even in the presence of hypovolemia. CVP can be increased in the presence of decreased ventricular compliance (cardiac failure), increased intrathoracic pressure (use of PEEP), increased right heart afterload and vasoconstriction. Thus, a high CVP either indicates hypovolemia or it indicates poor cardiac function in the presence of normovolemia.

by mansdocs.com



Figs. 5A and B: CVP waveform during spontaneous breathing and mechanical ventilation.

In a normal person with normal volume and normal CO, the CVP will be zero in the upright position. Hence, static measures of CVP are not very reliable.

Fluid Challenge

The only way one can know if a patient will respond to fluids while measuring CVP is by giving a fluid challenge. Weil and Henning had first described the fluid challenge technique, based on the 2–5 rule using CVP and the 3–7 rule for the PAOP.

With the availability of continuous monitoring techniques, the fluid challenge technique has been modified to incorporate four decision phases:

1. *Type of fluid*: Either crystalloid or colloid can be used. The choice of fluid can be decided based on the patient's clinical condition. However, based on the current evidence, it is preferable to avoid starch-based solutions in patients with septic shock.
2. *Rate of fluid administration*: More liberal fluid administration is recommended; 500–1000 mL crystalloid or 300–500 mL colloid over 30 minutes.
3. *Goals to be achieved for improvement in perfusion*: Set the targets for HR and blood pressure.
4. *Safety limits*: Set the limits for filling pressure that will be acceptable while giving a fluid challenge to minimize the risk of development of pulmonary edema.

The limitation of fluid challenge is that it is nonreversible and can increase the risk of fluid overload, especially in patients with cardiac or renal dysfunction.

Numerous studies and meta-analysis have failed to demonstrate the utility of CVP in predicting who will respond to fluid therapy. CVP is not a very good predictor of fluid responsiveness or circulating blood volume. CVP will be useful only if the values are very low or very high. Dynamic indices are superior in predicting fluid responsiveness.

by mansdocs.com

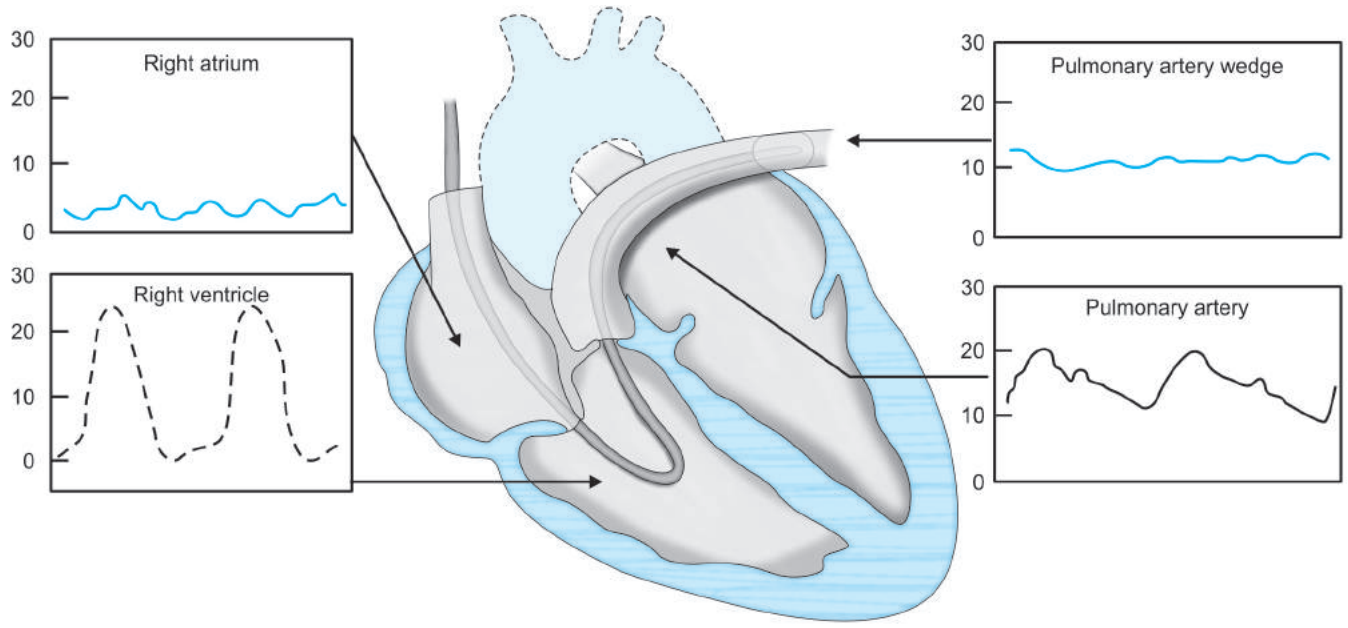


Fig. 6: Pulmonary artery catheter and waveforms in different chambers of heart during its passage.

Pulmonary Artery Catheter

It is a device used to measure the CO by the thermodilution technique. Various parameters which can be directly measured with pulmonary artery catheter (PAC) are RAP, PAOP, pulmonary artery pressure and mixed SvO_2. Other parameters which can be calculated include systemic vascular resistance (SVR), pulmonary vascular resistance, and SV and DO_2. A lot of information can be obtained from a single monitoring device. Some PACs have a heated filament located 15–25 cm from the catheter tip which allows continuous CO measurement by thermodilution technique.

The following waveforms will be seen while inserting the PAC. Initially, there will be CVP/right atrial trace, which will change to RV waveform as catheter tip advances to right ventricle, followed by the pulmonary artery trace and PAOP trace (similar to RAP trace). Normal values for RAP is 0–5 mm Hg, RV systolic pressure is 20–30 mm Hg and diastolic pressure is 0–5 mm Hg, pulmonary artery systolic pressure is 20–30 mm Hg and diastolic pressure is 8–12 mm Hg, and PAOP is 4–12 mm Hg (Fig. 6).

Though many newer monitoring techniques have been developed, PAC remains the gold standard for bedside hemodynamic monitoring of patients in shock. Though the PAC provides a lot of information, the use of PAC has not been shown to improve patient outcome because of the inability of the treating physicians to interpret and apply the data into clinical practice.

Dynamic Measures of Fluid Responsiveness

Monitoring pulse pressure changes in arterial waveform or SV variation in pulse contour analysis during mechanical ventilation in critically ill patients can provide important information about fluid responsiveness. The physiologic rationale behind this phenomenon is related to heart-lung interaction. In the initial stages of inspiration, the left ventricular SV increases because with positive pressure, the blood is squeezed from lungs increasing LV preload and there is a decrease in ventricular afterload due to a decrease in transmural pressure. This results in an increase in blood pressure during inspiratory phase of mechanical ventilation. Also due to positive intrathoracic pressure, there is a decrease in venous return and an increase in RV afterload. Thus, in the later part of inspiration, the RV output decreases, decreasing LV preload. Due to this the blood pressure decreases during expiratory phase of mechanical ventilation. These cyclical changes in left and RV output are more when the left ventricle is preload-dependent (operating on steep part of Frank-Starling curve). Thus, respiratory changes in pulse pressure or SV can be used to assess fluid responsiveness. ΔPP is the difference between the maximum (PP_{max}) and minimum (PP_{min}) pulse

by mansdocs.com

pressure divided by the average of the two values and expressed as percentage. ΔPP greater than or equal to 13% predicts fluid responsiveness in patients with septic shock receiving controlled mechanical ventilation. After fluid resuscitation, the decrease in pulse pressure correlates with increase in CO. Pulse pressure variation (PPV) is not reliable in patients with spontaneous efforts, those receiving low tidal volume ventilation and in patients with a respiratory compliance less than 30 mL/cm H_2O independent of the tidal volume.

End-Expiratory Occlusion Test

Dynamic indices are of limited utility in spontaneously breathing patients, in the presence of arrhythmias, patients receiving low tidal volume ventilation, use of high-frequency ventilation [respiratory rate >40 breaths/min], raised intra-abdominal pressures, open chest conditions and when the waveform is damped or distorted. Recently, alternative methods have been developed to assess fluid responsiveness which can be used in the above scenarios. In the end-expiratory occlusion test, the respiratory cycle is interrupted at end-expiration. This results in an increase in the cardiac preload as it interrupts the cyclic impediment to the venous return. If a 15-second end-expiratory occlusion test increases the pulse pressure or pulse contour-derived CO by 5%, it predicts fluid responsiveness.

Passive Leg Raising

Passive leg raising (PLR) is a reversible fluid challenge test. When patient's legs are elevated from 45° semirecumbent position, blood is mobilized from the legs and splanchnic circulation resulting in increase in the cardiac preload. The peak effects are seen in 1 minute, and the effects are not sustained even if the legs are kept elevated for a longer period. Hence, the monitoring device should be capable of tracking the hemodynamic changes within the time frame of PLR effects, i.e. 30–60s. Devices like esophageal Doppler, pulse contour-derived CO, aortic blood flow measured by echocardiography (ECHO), or CO measured by bioreactance can be used for real time hemodynamic measurements to assess PLR-induced fluid responsiveness. Several studies have shown that PLR-induced changes in arterial pressure are less accurate than PLR-induced changes in CO or SV. The limitation of this test is that it cannot be performed in situation where the patient cannot be mobilized like patients with head injury or in the operation theater.

Minimally Invasive Cardiac Output Monitoring

Pulmonary artery catheter had been the mainstay of hemodynamic monitoring till end of last century. However, some degree of skill is required to position the PAC as well as to interpret the data accurately. This may not be available at all institutions at all times. Also, PACs have a number of disadvantages, namely infection, pulmonary artery rupture, arrhythmias, thrombosis and embolism. To overcome these problems, many new devices which are less invasive than PAC but capable of monitoring continuous CO have been developed. Each of these devices utilizes different physiologic principles to determine CO and has its own limitations.

Some of these less invasive monitoring techniques make use of arterial waveform to continuously measure the CO. There are main three monitoring systems in market which utilize arterial pressure wave.

1. *The PiCCO* system uses a thermostat-tipped arterial line in a proximal artery (radial, femoral, brachial or axillaries) to monitor the arterial waveform. A central venous catheter is used to calibrate the system using a transpulmonary thermodilution similar to one used in PAC. An algorithm is used to determine the CO by integrating the area under the curve of the arterial pressure. This device should be calibrated every 8 hours or more frequently in hemodynamically unstable patients for better reliability. With PiCCO, along with continuous cardiac output (CCO), one can also obtain dynamic parameters of preload like stroke volume variation (SVV), PPV and systolic pressure variation (SPV), and volumetric parameters like global end-diastolic volume, extravascular lung water (EVLW) and intrathoracic blood volume. EVLW is useful for differentiating and quantifying lung edema. Normally, it should be less than 8 mL/kg. The PiCCO device has been extensively studied and compared with pulmonary artery thermodilution-derived CO measurements with very good correlation. This strong correlation remained even when significant variations in hemodynamic and vascular tone were present.
2. *The FloTrac/Vigileo* system (Edwards Lifesciences) also utilizes a blood flow sensor, attached to a standard arterial catheter. However, this does not require external calibration. It uses an algorithm which integrates multiple characteristics of arterial pressure waveform with patient-specific demographic data and this

by mansdocs.com

algorithm is continuously updated. Using FloTrac, one can obtain CCO, SV and SVV. Cardiac output is calculated every 20 seconds.

3. *The LiDCO* monitor (LiDCO, UK) uses pulse power analysis rather than pulse contour analysis. It uses an algorithm based on the law of conservation of mass for CCO calculation. The pulse power, rather than pulse contour, is measured. By using the assumption that net power has a linear relationship with net flow, an algorithm is used to calculate CO. A standard arterial line only is required. Like PiCCO, even LiDCO needs external calibration using lithium that needs to be repeated every 8 hours for better reliability. It is contraindicated in patients on lithium therapy or within 30 minutes of neuromuscular blocker administration.

All pulse contour analysis devices are unreliable in the presence of arrhythmias, ventricular assist device and intra-aortic balloon pump.

Aortic Doppler

Cardiac output can be estimated using Doppler ultrasound to determine the flow of blood through the aorta. Most devices in current practice use a Doppler probe inserted into the esophagus to measure descending aortic flow. The velocity-time integral is calculated from the area under the velocity-time curve in descending thoracic aorta and used as the stroke distance. The shape of the waveform allows assessment of the LV preload, contractility and afterload. The base of the wave gives the flow time (i.e. the LV ejection time) which is corrected for HR to give the corrected flow time (FTc). The height of the waveform gives the peak velocity, and the upstroke of the wave provides the mean acceleration. These are the parameters from which the remaining cardiovascular indices, such as SV, CO and SVR, are derived. An estimate of aortic cross-sectional area (CSA) is taken either from a monogram (height, weight and age) or measured using transthoracic ECHO. Estimation of CSA may be an important source of error for this method of CO measurement. Also, the probe position is critical in reducing measurement error for blood flow measurement. This device has been extensively used in intraoperative period to decide optimal fluid therapy for patients undergoing various surgeries; however, in critically ill patients, CO measurements have shown variable results. A major disadvantage of the Doppler technique is the need for probe placement in the esophagus, effectively limiting its use to mechanically ventilated patients. Paris consensus conference held in 2006 does not recommend routine measurement of CO for patients with shock (Level 1B).

Echocardiography: Though transthoracic ECHO does not quantify CO precisely, it provides noninvasive qualitative assessment of right and left heart filling, contractility, valvular function and pericardial disease. Visualizing inferior vena cava (IVC) and change in its diameter with respiration can be used to decide volume status. When available and performed/interpreted correctly, ECHO can identify cause of shock, and allow early therapies. Paris consensus conference held in 2006 suggests considering ECHO or measurement of CO for diagnosis in patients with clinical evidence of ventricular failure and persistent shock despite adequate fluid resuscitation (Level 2B).

MONITORING MARKERS OF PERFUSION (DOWNSTREAM MARKERS)

Serum Lactates

In a normal steady state with adequate tissue resources and oxygen, cellular energy is produced aerobically by means of the citric acid cycle. However, in situations of inadequate tissue perfusion or inadequate DO_2, it undergoes anaerobic metabolism to create some energy.

Lactate and Critical Illness

The normal plasma lactate concentration is 0.3–1.3 mmol/L. Plasma concentrations represent a balance between lactate production and lactate metabolism. Under stable conditions, glucose is converted to pyruvate, producing 2 ATP. Pyruvate enters the Krebs cycle and is subsequently fully oxidized to CO_2, generating up to 36 ATP. Under normal conditions, lactate is produced by tissues that lack mitochondria, e.g. red blood cells. The liver removes 70% of lactate. Mitochondria-rich tissues such as skeletal and cardiac myocytes and proximal renal tubule cells remove the rest of the lactate by converting it to pyruvate. Less than 5% of lactate is renally excreted.

Hyperlactatemia (>5 mmol/L) is conventionally divided into:

- Type A, in which tissue hypoxia results in faster production than removal.
- Type B, in which overt tissue hypoxia does not play a role.

by mansdocs.com

Type B has been further subdivided depending on whether it is caused by underlying disease (B1), drugs and toxins (B2) or inborn errors of metabolism (B3).

In a patient with hyperlactatemia, if the main pathophysiological mechanism is increased production caused by hypoxia and tissue hypoperfusion (i.e. type A lactic acidosis), monitoring of blood lactate may indicate the adequacy of tissue perfusion. Conversely, if the pathophysiological process is mainly lactate underutilization related to acute liver failure, serial lactate determination may provide useful information on liver function. If however hyperlactatemia results from a combination of overproduction and underutilization, more specific methods are needed to assess these processes.

Causes of elevated lactate other than hypoperfusion:

- Increased glycolysis
- Liver dysfunction
- Alcohol intoxication
- HIV patients
- D-lactic acidosis
- Metformin
- *Warburg effect*: Very high levels of lactate and lactate dehydrogenase are found in patients with lymphoma which responds to chemotherapy.
- *Renal replacement therapy*: Using lactate-containing buffer solutions can cause transient hyperlactatemia.

Rationale for Lactate Measurement

When the DO_2 decreases and reaches a critical value, the VO_2 becomes supply-dependent, and any further reduction in the delivery switches the metabolism from aerobic to anaerobic giving rise to increased production of lactate. Conditions with poor tissue perfusion would also lead to decreased clearance of lactates and eventually give rise to hyperlactatemia. The utility of serum lactate as a tool to identify the most seriously ill patients and to monitor their response to treatment has long been recognized. Increased blood lactate levels and their failure to normalize during treatment of shock have been associated with increased morbidity and mortality and can provide valuable clinical information. Recent study by Jansen and coworkers has shown significantly reduced hospital mortality when adjusting for predefined risk factors using lactate-guided therapy in patients with hyperlactatemia on ICU admission. Paris consensus conference held in 2006 suggests serial measurements of lactates and/or base deficit as a predictor of outcome (Level 2B).

How and where to measure lactate levels: The sample can be drawn from arterial or venous capillary; it does not seem to affect the results much. However, especially when targeting changes in lactate levels in relatively short intervals, it is not appropriate to interchange measurement devices (point of care vs laboratory) and also sampling site. To prevent an in vitro rise in blood lactate levels, especially when leukocytosis or a high hematocrit is present, a maximum turnaround time of 15 minutes or storage of the sample on ice is appropriate. Alternatively, tubes containing fluoride, a potent inhibitor of in vitro glycolysis, should be used.

Venous Oximetry

Sustained tissue hypoxia is one of the most important cofactors in the development of multiorgan failure. Oxygen delivery-tissue demand mismatch can be measured by venous oximetry. The two principal sources for venous oximetry at the bedside are either a PAC or a central venous catheter, generating mixed (SvO_2) and central venous oxygen saturation ($ScvO_2$) measurements. While SvO_2 is the true mixed venous parameter, indicating global oxidative balance and correlating best with DO_2 and utilization (DO_2/VO_2), $ScvO_2$ is its constituent part and as such only representative of the organs of the upper body.

Rationale for Venous Oximetry

Oxygen consumption can be described by the Fick equation as $VO_2 = Q \times (CaO_2 - CvO_2)$; where, Q is the CO, CaO_2 is arterial content of oxygen in blood, and CvO_2 is venous oxygen content of blood. The above equation can be further derived to express the relationship between SvO_2 and CO.

$VO_2 = Q \times 1.34 \times Hb \times (SaO_2 - SvO_2)$, rearranging this equation:

$SvO_2 = SaO_2 - VO_2/Q \times 1.34 \times Hb$

$SvO_2 = SaO_2 - VO_2/DO_2$

If the VO_2 increases, the CO increases to meet the increased demand. If, however, the CO does not increase then the tissues extract more oxygen and as a result, the blood returning to the heart has decreased venous oxygen saturation. Thus, SvO_2 is a direct reflection of balance between supply and demand.

Oxygen extraction ratio (O_2 ER) is the ratio of O_2 uptake to O_2 delivery, i.e. oxygen taken up by the tissues is a fraction of the oxygen delivered to the microcirculation.

$$O_2\ ER = VO_2/DO_2$$

by mansdocs.com

Table 1: Causes of changes in mixed venous oxygen saturation.

Increased mixed venous oxygen saturation	*Decreased mixed venous oxygen saturation*
↓O_2 consumption	*↑O_2 consumption*
Sedation	*Physiological*
Analgesia	Exercise
Hypothermia	*Pathological*
Mechanical ventilation	Agitation
	Pain
	Fever
	Shivering
	Respiratory failure
	↑Metabolic demand
↓O_2 extraction	
Shunting (sepsis)	
Cell death	
↑O_2 delivery	*↓O_2 delivery*
Oxygen therapy	Anemia
Blood transfusion	Hemorrhage
Intravenous fluid	Hypoxia
Inotropics	Hypovolemia
↑Cardiac output	Heart failure

Normally, O_2 ER is 0.3 or 30%; only a fraction is required to support aerobic metabolism under normal circumstances. So, there is a reserve of about 70% oxygen, and body can utilize this reserve in the face of decreased delivery without initially compromising aerobic respiration. The fall or rise in SvO_2 can be due to increased demands or decreased supply, or increased supply or decreased demand respectively (Table 1).

During exercise, SvO_2 normally decreases despite increasing DO_2. Therefore, a drop in SvO_2 or $ScvO_2$ does not necessarily mean that there is tissue hypoxia. The magnitude of the decrease indicates the extent to which the physiological reserves are stressed. In healthy individuals, anaerobic metabolism may occur when SvO_2 drops below its normal value of 75% to 30–40%.

The normal range for SvO_2 is 65–75%. Low SvO_2 is suggestive of poor outcome, whereas normal or supranormal SvO_2 values do not mean adequate tissue oxygenation. For example, if there is shunting of blood or cell death, the tissue is not capable of extracting oxygen; as a result, the venous return may have high oxygen content despite persistent cellular hypoxia.

Relationship between Central Venous Oxygen Saturation and Mixed Venous Oxygen Saturation

Measurement of SvO_2 requires insertion of PAC. Recently, insertion of PAC has become unpopular because of the harm caused by insertion and misinterpretation of the data derived from it.

The tip of the central venous catheter usually lies at the junction of the SVC and the RA or in the SVC. The sample drawn from here represents the venous blood from upper body (head and upper extremities). In healthy patients, the blood in IVC has higher oxygen saturation compared to that in the SVC, because of lower O_2 extraction vascular beds (renal blood flow, portal flow, hepatic blood flow) draining into IVC. The oxygen extraction is lower because these organs utilize the blood flow for nonoxidative phosphorylation. A normal value for SvO_2 is in the range of 65–75%. Thus, $ScvO_2$, in normal individuals, is usually lower by 2–3% than the SvO_2.

The absolute values of SvO_2 and $ScvO_2$ differ but the changes in SvO_2 are accompanied by parallel changes in $ScvO_2$ as demonstrated in an anesthetized dog model under various clinical conditions, such as hypoxia, hemorrhagic shock, fluid resuscitation and hyperoxia. Similar correlation was demonstrated in critically ill patients over 1,000 hours by K Reinhart and colleagues.

Factors that may affect the difference between SvO_2 and $ScvO_2$: The physiological difference between SvO_2 and $ScvO_2$ may be affected by:

- *General anesthesia/sedation*: $ScvO_2$ may be higher than SvO_2. Both general anesthesia and sedation reduce the cerebral metabolism and cerebral extraction ratio, and thus increasing the oxygen saturation in the SVC.
- *Redistribution of blood flow in shock states*: There is reversal of the physiologic difference between the SvO_2 and $ScvO_2$ in shock states, i.e. $ScvO_2$ greater than SvO_2. In shock states, during the initial stage, the blood is diverted from the mesenteric and renal beds to the heart and brain, preserving cerebral blood flow, as the blood flow to the splanchnic bed decreases, there is increased extraction of O_2 by the splanchnic bed leading to lower than normal saturation of blood in the IVC and therefore $ScvO_2$ greater than SvO_2. If, however, appropriate and timely interventions are not done, there is delayed fall in $ScvO_2$ due to failing compensatory mechanisms. This is seen in septic, hemorrhagic and neurogenic shock, and in heart failure.
- *Microcirculatory shunting or cell death*: There is ineffective/impaired oxygen extraction due to microcirculatory shunting; as a result, the oxygen saturation in the capillary blood is close to arterial level and thus saturation of the venous blood returning to the heart increases. Similarly, decreased oxygen extraction occurs in cell death.

by mansdocs.com

Clinical Utility of Venous Oximetry

- *Cardiogenic shock*: Patients with cardiogenic shock or LV dysfunction/failure have lower SvO_2 than $ScvO_2$. Patients with cardiogenic shock, in situations of increased demand, cannot increase the delivery any further; as a consequence, they increase the oxygen extraction to meet the increased demands resulting in lower SvO_2. So, any further decrease in SvO_2 is an indication of cardiac deterioration. Correlation between $ScvO_2$ and SvO_2 is poor in heart failure but is good in patients with myocardial infarction. During cardiopulmonary resuscitation, $ScvO_2$ of 72% is highly predictive for return of spontaneous circulation. However, in patients after prolonged cardiac arrest, venous hyperoxia with a $ScvO_2$ greater than 80% is indicative of impaired oxygen utilization.
- *Sepsis and septic shock*: is complicated by development of multiorgan failure, and tissue hypoxia is one of the important reasons for organ failure. In the landmark study by Rivers et al., patients with sepsis and septic shock who were resuscitated early and aggressively guided by $ScvO_2$ greater than 70% in addition to maintaining target levels of CVP, MAP and urine output had a 15% absolute reduction in mortality compared to the same treatment without $ScvO_2$ monitoring. Following this landmark trial, the surviving sepsis guidelines recommended a goal of SvO_2 or $ScvO_2$ greater than 70% as a goal of resuscitation.
- *Perioperative period*: Immediately following surgery, there can be a significant drop in $ScvO_2$ probably related to increased VO_2 in the immediate postoperative period due to pain, emergence from anesthesia, and shivering. However, reductions in $ScvO_2$ after surgery were demonstrated to be independently associated with postoperative complications. However, many questions remain unanswered, such as, what should be the ideal cutoff value to target as studies have demonstrated values between 64% and 73%, and how long should one continue to monitor $ScvO_2$ in the postoperative period, and lastly, what should be the optimal management strategy considering various factors that can affect VO_2 in the postoperative period. Nevertheless, a drop in $ScvO_2$ in the perioperative period cannot be ignored and should warrant appropriate management.
- *Trauma*: $ScvO_2$ has been suggested to be used as a target of resuscitation. $ScvO_2$ less than 65%, in patients with major trauma and head injury, during the initial 24 hours following admission has been demonstrated to be associated with higher mortality and prolonged hospitalization.

Limitations of Venous Oximetry

Venous oximetry can reflect the adequacy of tissue oxygenation only if the tissue is still capable of extracting O_2. One must remember that the absolute values of $ScvO_2$ and SvO_2 are not interchangeable. The difference between these two parameters is influenced by the presence of left-to-right shunts, incomplete mixing of venous blood, oxygen extraction in the renal and the splanchnic beds, redistribution of blood flow through the upper and lower body, level of consciousness (anesthesia) and myocardial VO_2.

The reliability of $ScvO_2$ is also dependent on the position of the tip of the catheter, with right atrial measurements closely approximating SvO_2 and high vena cava measurements often deviating substantially from SvO_2. In general, SvO_2 is more useful when the value is below normal, even though in these conditions, it may not reflect a hemodynamic problem. Central venous oxygen saturation should not be used alone in the assessment of the cardiovascular system but combined with other hemodynamic parameters and indicators of organ perfusion, such as serum lactate concentration and urine output.

MONITORING MICROCIRCULATION

Microcirculation is the part of the circulation where nutrients, water, gases (such as oxygen), hormones and waste products are exchanged between the blood and cells. The microcirculation also functions as a volume reservoir for blood, so that the microcirculation plays an important role in regulating preload and thus CO. An adequate blood flow within these microvessels is a prerequisite for normal organ perfusion. More and more data suggest hypoperfusion of microcirculation may be an etiologic factor in the pathogenesis of multiple organ failure and may contribute to mortality in a considerable proportion of patients with circulatory shock.

There are various techniques by which one can monitor regional microcirculation:

Gastric Tonometry

Traditional global parameters of hemodynamic monitoring fail to identify regional hypoperfusion. Splanchnic perfusion gets affected in early compensated shock. The gut being very sensitive to ischemia, periods of hypoperfusion

by mansdocs.com

lead to release of inflammatory cytokines and bacterial translocation, thereby causing damage in remote organs. Monitoring perfusion to gut helps in identifying gut hypoperfusion at earliest, and resuscitation directed at improving gut perfusion can help in improving outcome. Buffering of hydrogen ions generated due to intracellular acidosis releases CO_2. This increased production of CO_2 along with diminished washout due to poor circulation leads to increase in intracellular CO_2 tissue. Local tissue hypercarbia has been shown to reflect splanchnic organ dysoxia during states of circulatory shock. Since stomach is most accessible part of splanchnic region, gastric tonometry attempts to determine the perfusion status of the gastric mucosa using measurements of local PCO_2 and intramucosal pH (pHi). The gastric mucosal PCO_2 is measured by using either saline tonometry or air tonometry. Studies have shown that pHi reduced much before the traditional markers of hypoperfusion became evident. However, pHi-directed resuscitation did not improve mortality. Persistently low pHi predicted mortality, and improvement in pHi suggested chances of good outcome.

Sublingual Capnometry

Due to technical problems associated with measurement of gastric tonometry, researchers started exploring other sites for tissue CO_2 monitoring. Since sublingual region is part of gut and easily accessible, sublingual PCO_2 measurement ($P_{SL}CO_2$) can be used to assess adequacy of splanchnic circulation. Studies have shown that gastric PCO_2 correlates well with $P_{SL}CO_2$ and elevated $P_{SL}CO_2$ predict mortality.

Indocyanine Green Clearance

The hepatosplanchnic system is considered to play a major role in the development of sepsis and multiple-organ failure. Thus, early and sufficient therapies of hepatosplanchnic ischemia or hypoxia are of major clinical importance. After intravenous injection, indocyanine green (ICG) is nearly completely eliminated unchanged by the liver into the bile, without enterohepatic recirculation. Studies have shown that ICG plasma disappearance rate reflects ICG blood clearance sufficiently accurately in critically ill patients and may be used as a surrogate for the hepatic blood flow.

Near Infrared Spectroscopy

Principle here is same as pulse oxymetry; however, while pulse oximetry monitors hemoglobin only in arterial part of blood, near infrared spectroscopy (NIRS) monitors the total tissue oxy- and deoxyhemoglobin in quantitative and qualitative terms. The NIRS probe emits lights with several wavelengths between 700 nm and 850 nm and measures the reflected light from fixed depth (within few centimeters from skin). The main determinants of signal are small vessels in microcirculation. Thennar eminence is a preferred site due to relatively thin fat tissue over muscle. In presence of hypovolemia activation of sympathetic nervous system decreases blood flow to thennar muscles with increased oxygen extraction and thus decreased tissue oxygen saturation; however, in patients with septic shock due to substantial microvascular disturbances, NIRS interpretation is complex and this tool is still being used mostly in research settings.

New technology, namely *sidestream dark field imaging and orthogonal polarization spectral (OPS) imaging* allows noninvasive observation of human microcirculation in all accessible tissue surfaces. Sublingual region is most favored region, as embryologically, it is part of foregut and thus representative of splanchnic circulation, easily accessible and is covered with only thin layer of mucosa. Studies have found that the density of all vessels and proportion of perfused small vessels (diameter ≤ 20 μm) are significantly less in septic patients and patients with cardiogenic shock. This tool is still used in research setting and not widely used in clinical practice. Also, whether interventions specifically aimed at correcting regional or microcirculatory variables may improve outcome is still not determined. Paris consensus conference held in 2006 does not recommend routine use of gastric tonometry, sublingual capnography, OPS imaging and other techniques to assess regional or microcirculation (Level 1B).

CHOOSING PATIENT-TAILORED HEMODYNAMIC MONITORING

Selection of monitoring tool will depend on type of patient and underlying pathophysiology. The sicker the patient, the lesser is the margin of error, greater is the need for accurate hemodynamic parameters and the greater likelihood of invasive technique. For patients at high risk of pulmonary edema, hemodynamic monitoring that gives measurements of EVLW may be chosen to optimize fluid therapy. Femoral artery catheterization would be contraindicated in patients with aortofemoral bypass patients. Esophageal Doppler monitoring or transesophageal ECHO will obviously be not feasible in patients with esophageal diseases. In patients with chronic obstructive pulmonary

by mansdocs.com

disease or thick chest wall obtaining good ECHO window may be extremely difficult limiting use of transthoracic ECHO. Pulse-contour methods cannot be used in presence of significant arrhythmias, aortic valve regurgitation or in presence of intra-aortic balloon pump. In mechanically ventilated patients with low tidal volume or in patients with right ventricle dysfunction, dynamic measures of fluid responsiveness are unreliable and volumetric assessment as done using PiCCO may be more useful.

SUMMARY

Hemodynamic monitoring is a diagnostic tool, and no diagnostic tool can improve outcome unless coupled with effective therapeutic measure. As technological advancement takes place, newer and better monitoring tools would be available; however, each tool will have its own shortcomings, and user should be aware of this.

BIBLIOGRAPHY

1. Antonelli M, Levy M, Andrews PJ, et al, Manthous C, et al. Hemodynamic monitoring in shock and implications for management International Consensus Conference, Paris, France, 27–28 April 2006. Intensive Care Med. 2007;33: 575-90.
2. Bloos F, Reinhart K. Venous oximetry. Intensive Care Med. 2005;31(7):911-3.
3. Bourgoin A, Leone M, Delmas A, et al. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. Crit Care Med. 2005; 33:780-6.
4. De Backer D, Taccone FS, Holsten R, et al. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. Anesthesiology. 2009;110:1092-7.
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. Crit Care Med. 2012;41(2): 580-637.
6. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134: 172-8.
7. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37:2642-7.
8. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121:2000-8.
9. Monnet X, Teboul JL. Assessment of volume responsiveness during mechanical ventilation: recent advances. Crit Care. 2013;17:217.
10. Pinsky M, Payen D. Functional haemodynamic monitoring. Crit Care. 2005;9(6):566-72.
11. Vincent JL, Weil MH. Fluid challenge revisited. Crit Care Med. 2006;34(5):1333-7.

by mansdocs.com

CHAPTER

4

Fluid Balance in Critically Ill Patients

Shikha Panwar

INTRODUCTION

Fluid balance is closely related to acid base balance which is maintained by kidneys and various neuroendocrine and autonomic mechanisms. The normal fluid and acid base balance can be disturbed by various diseases. Disease is accompanied not only by changes in the balance of water and electrolytes between the body and its environment (external balance) but also by changes in the relationship between the fluid compartments within the body and the fluxes between them (internal balance). Disease also influences the cardiovascular and renal responses to fluid and electrolyte intake through autonomic and neuroendocrine mechanisms. Intake of fluid and electrolytes versus the output from the kidneys, the gastrointestinal tract, and the skin and lungs (insensible loss) all are important for an integrated balance of fluids.

In the human body the total body water is around 60% of total body weight. It is then further divided as per its distribution to 20% extracellular and 40% intracellular compartment which are again subdivided into the intravascular 6% (within the circulation) and the interstitial 14% fluid (extravascular fluid surrounding the cells) (Fig. 1).

The volume of fluid (water) within a compartment is determined by cell membrane permeability, osmolarity and electroneutrality. Cell membrane permeability refers to the ability of a cell membrane to allow certain substances such as water and urea to pass freely, while charged ions such as sodium cannot cross the membrane and are trapped on one side of it. Osmolarity is a property

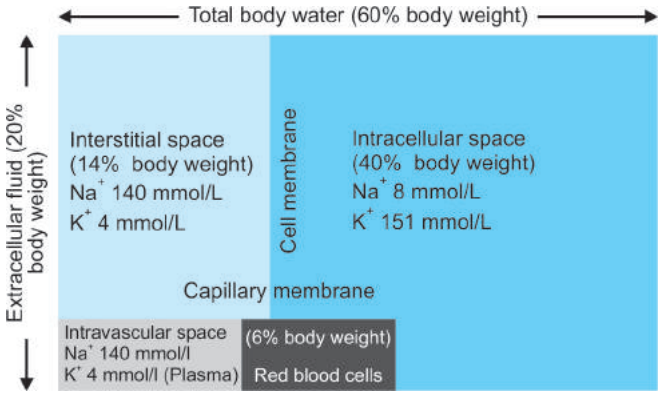


Fig.1: Body fluid compartments with approximate electrolyte concentrations. Red blood cells (hematocrit) account for approximately 45% of total intravascular volume.

of particles in solution. If a substance can dissociate in solution, it may contribute more than one equivalent to the osmolarity of the solution. For instance, NaCl will dissociate into two osmotically active ions: Na^+ and Cl^-. One millimolar NaCl yields a 2 milliosmolar solution. Electroneutrality means that the overall number of positive and negative charges balances. For instance, in conditions like renal tubular acidosis where carbonic acid is lost, chloride is retained leading to a hyperchloremic state. Expected osmolarity of plasma can be calculated according to the following formula:

Plasma osmolarity = 2(Na)+(Glucose/18)+(BUN/2.8) {Glucose and BUN are measured in mg/dl).

Concentration of sodium is the major determinant of serum osmolarity. Normal serum osmolarity ranges from about 280 mOsm to 295 mOsm.

by mansdocs.com

Components of the extracellular fluid (ECF) are separated by the capillary membrane, with its micropores, which allow only a slow escape rate of albumin (5% per hour), which is then returned to the circulation via the lymphatics at the same rate, thereby maintaining a steady state of equilibrium. Osmotic forces of "trapped" solutes govern water distribution between compartments and volume. While the hydrostatic pressure within the circulation tends to drive fluid out, the oncotic pressure of the plasma proteins, e.g. albumin, draws fluid in and maintains the relative constancy of the plasma volume as a proportion of the ECF (Starling effect).

There is also a clinically important flux of fluid and electrolytes between the ECF and the gastrointestinal tract involving active secretion and reabsorption of digestive juices. In health there is a mechanism to ensure a constant relationship between them, with a constant flux between these various spaces to maintain the internal fluid balance.

Organs, which sense the changes in osmolality of plasma (osmoreceptors), are located in the hypothalamus and signal the posterior pituitary gland to increase or decrease its secretion of vasopressin or antidiuretic hormone (ADH). Dilution of the ECF, including plasma, by intake of water or fluid of osmolality lower than plasma, causes ADH secretion to fall, so that the distal tubules of the renal glomeruli excrete more water and produce a dilute urine (this dilution requires the permissive effect of glucocorticoid upon the distal tubules and is, therefore, lost in adrenal insufficiency—one of the reasons for the hyponatremia of Addison's disease). Conversely, dehydration causes the ECF to become more concentrated, ADH secretion rises and the renal tubules reabsorb more water, producing concentrated urine. In response to dehydration, the normal kidney can concentrate urea in the urine up to a hundredfold, so that the normal daily production of urea during protein metabolism can be excreted in as little as 500 mL of urine (Table 1).

Table 1: Distribution of various solutes in intracellular fluid (ICF) and extracellular fluid (ECF).

	ICF (mEq/L)	*ECF (mEq/L)*
Cations	Potassium (150–154)	Sodium (135–140)
	Sodium (6–10)	Calcium (5)
	Magnesium (40)	Potassium (4–5)
		Magnesium (3)
Anions	Organic phosphate (100–06)	Chloride (103–105)
	Protein (40–60)	Bicarbonate (24–27)
	Bicarbonate (10–13)	Phosphate (3–5)
	Organic acids (4)	Organic acids (2–5)
	Sulfate (17)	Sulfate (4)

SODIUM

Since the integrity of the ECF volume and its proportion of the total body water are largely dependent on the osmotic effect of Na^+ and its accompanying anions, it is important that the kidneys maintain Na^+ balance within narrow limits. If salt depletion occurs, the ECF along with the plasma volume decreases. Pressure sensors in the circulation are then stimulated and these excite renin secretion by the kidney. This, in turn, stimulates aldosterone secretion by the adrenal gland, which acts on the renal tubules, causing them to reabsorb and conserve Na^+. Conversely, if the intake of Na^+ is excessive, the renin-aldosterone system switches off, allowing more Na^+ to be excreted, until normal balance is restored. The mechanism for salt conservation is extremely efficient and the kidney can reduce the concentration of Na^+ in the urine to less than 5 mmol/L. The mechanism for maintaining sodium balance may become disturbed in disease, leading to Na^+ deficiency or, more commonly, to excessive sodium retention, with consequent edema and adverse clinical outcome.

POTASSIUM

Although only a small proportion of the body's K^+ is in the extracellular space, its concentration has to be maintained within narrow limits (3.5–5.3 mmol/L) to avoid the risk of muscular dysfunction or potentially fatal cardiac events. This is achieved by exchange of K^+ in the renal tubules for Na^+ or H^+, allowing more or less K^+ to be excreted. In the presence of K^+ deficiency, H^+ ion reabsorption is impaired, leading to hyperchloremic acidosis.

Pathophysiology

In critically ill patients the normal homeostatic mechanisms are deranged and basic life preserving senses, such as thirst and hunger, may be abolished by disease itself or may be hindered by sedation or other treatment modalities. As a result, survival of the critically ill patient depends on the administration of appropriate volume of fluid and quantities of electrolytes and nutrition. Basal requirement apart from the ongoing disease process has to be met by the intravenous (IV) fluid. So the fluid requirement by a patient can be assessed by dividing it into maintenance,

by mansdocs.com

replacement and resuscitation fluid. If the patient is clinically stable and does not have excess losses above insensible loss he needs only maintenance fluid which is approximately 30mL/kg/24 hours. Patients having to fast for over 8–12 hours should be started on IV maintenance fluid. Replacement of ongoing losses, either previous or current has to be added to the maintenance fluids according to the disease pathology. If losses are predicted, it is best to replace these later rather than give extra fluid in anticipation of losses which may not occur. This fluid is in addition to maintenance fluid. If the patient is hypovolemic as a result of dehydration, blood loss or sepsis he requires urgent correction of intravascular fluid depletion so he has to be given rapid resuscitation fluids according to guidelines.

Intravenous fluids are chemically prepared solutions that are administered to the patient. They are tailored to the body's needs and used to replace lost fluid and/or aid in the delivery of IV medications venous fluids. The choice of IV fluid will depend upon a number of factors. The most important is the type of fluid that has been lost, the electrolyte status and the adverse effects of each IV fluid.

Intravenous fluids come in two different forms: (1) colloids and (2) crystalloids.

Colloid solutions are IV fluids that contain solutes in the form of large proteins or other similarly sized molecules. The proteins and molecules are so large that they cannot pass through the walls of the capillaries and onto the cells. Accordingly, colloids remain in the blood vessels for long periods of time and can significantly restore the intravascular volume faster than crystalloids and with lesser quantity. The proteins also have the ability to attract water from the cells into the blood vessels. However, although the movement of water from the cells into the bloodstream may be beneficial in the short-term, continual movement in this direction can cause the cells to lose too much water and become dehydrated.

During sepsis, the membrane permeability is altered resulting in greater movement of colloids into the interstitium. Colloids are expensive, have specific storage requirements, and have a short shelf life.

The clinical relevance of the theoretical advantages of colloids (with regards to effects on the microvasculature) was questioned as early as the late 1970s. The saline versus albumin fluid evaluation (SAFE) trial compared the effects of 4% albumin versus normal saline[1] in 6,997 critically ill patients and found no difference in the primary outcome (all-cause mortality at 28 days). Subgroup analysis revealed a possible association between the use of albumin and increased mortality in patients with traumatic brain injury. It should be noted that this post hoc analysis was performed on only 492 patients or 7% of the original study population. In a follow-up report of 460 traumatic brain injury patients from the original SAFE trial, the association of albumin with higher mortality rates in this group persisted at 2 years following randomization. The current consensus statement of the European Society of Intensive Care Medicine already discourages the use of hydroxyethyl starches (HES) in patients with severe sepsis or acute kidney disease.

Resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4% (95% confidence interval 0–8%), or four extra deaths for every 100 patients resuscitated. As colloids are not associated with improved survival and are considerably more expensive than crystalloids, it is hard to see how their continued use outside randomized controlled trials in subsets of patients of particular concern can be justified.[2]

- Commonly used colloid solutions include plasma protein fraction, salt poor albumin, dextran and hetastarch.

Crystalloid solutions are composed of small particles dissolved in water, which pass easily through the endothelial barrier. Crystalloids contain electrolytes (e.g. sodium, potassium, calcium, chloride) but lack the large proteins and molecules found in colloids. Crystalloids come in many preparations and are classified according to their "tonicity". A crystalloid's tonicity describes the concentration of electrolytes (solutes) dissolved in the water, as compared with that of body *plasma* (fluid surrounding the cells).

Isotonic crystalloids have a tonicity *equal* to the body plasma. When administered to a normally hydrated patient, isotonic crystalloids do not cause a significant shift of water between the compartments.

Hypertonic crystalloids have a tonicity *higher* than the body plasma. The administration of a hypertonic crystalloid causes water to shift from the extravascular spaces into the bloodstream, increasing the intravascular volume. This osmotic shift occurs as the body attempts to dilute the higher concentration of electrolytes contained within the IV fluid by moving water into the intravascular space.

Hypotonic crystalloids have a tonicity *lower* than the body plasma. The administration of a hypotonic crystalloid causes water to shift from the intravascular space to the extravascular space, and eventually into the tissue cells. Because the IV solution being administered is hypotonic, it creates an environment where the extravascular

by mansdocs.com

Table 2: Composition of common intravenous fluids.

Electrolyte	*Plasma*	*0.9% NaCl*	*Lactated Ringer's*	*Dextrose 5%*	*Human albumin*	*Hetastarch*
Sodium	140	154	131	0	145	154
Potassium	5	0	5	0	0	0
Chloride	100	154	111	0	95	154
Calcium	2.2	0	2	0	0	0
Magnesium	1	0	1	0	0	0
Bicarbonate	24	0	0	0	0	0
Lactate	1		28	0	0	0
mOsm/L		308	273	278	300	310

Table 3: Volume of infusion required to expand the plasma volume by 1 litre.[4]

	Infused Volume (mL)	*Interstitial Volume (mL)*	*Intracellular Volume (mL)*
0.9% normal saline	4,700	+3,700	
5% dextrose	14,000	+3,700	+9,300
5% albumin	1,000		
25% albumin	250	–750	

spaces have higher concentrations of electrolytes. The osmotic change results in the body moving water from the intravascular space to the cells in an attempt to dilute the electrolytes.

Of the different types of IV solutions, crystalloids are the mainstay of resuscitation (Table 2). The most common isotonic solutions used are:

- *Lactated Ringer's* (LR) is an isotonic crystalloid that contains NaCl, potassium chloride, calcium chloride, and sodium lactate in sterile water.
- *Normal saline solution* (NS) is an isotonic crystalloid that contains 0.9% NaCl (salt) in sterile water.
- *Dextrose 5% in water* (D5W) is packaged as an isotonic carbohydrate (sugar solution) that contains glucose (sugar) as the solute.

Lactated Ringer's and NS are commonly used for fluid replacement because of their immediate ability to expand the volume of circulating blood. However, over the course of about 1 hour, approximately two-thirds of these IV fluids eventually leave the blood vessels and move into the cells. The ability of a solution to expand the plasma volume is dependent on its volume of distribution and the metabolic fate of the solute, so that while colloids are mainly distributed in the intravascular compartment, once the dextrose is metabolized, dextrose containing solutions are distributed through the total body water and hence have a limited and transient blood volume expanding capacity (Table 3 and Fig. 2).

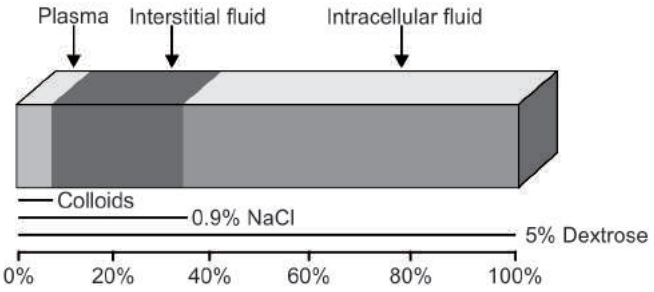


Fig. 2: Distribution of infused fluids in the body water compartments.

One myth regarding crystalloid selection deserves further assessment—calcium-containing solutions are not absolutely contraindicated in the setting of transfusion. Most studies demonstrating clotting were based on citrate-phosphate-dextrose-adenine preserved packed red blood cells; newer preservatives, such as AS-3, contain less plasma and more citrate, and are much less likely to be overwhelmed by the small amount of calcium present in isotonic crystalloids.[3]

The cornerstone of treating patients with shock remains as it has for decades—IV fluids. Surprisingly, dosing IV fluid during resuscitation of shock remains largely empirical.

by mansdocs.com

Too little fluid may result in tissue hypoperfusion and worsen organ dysfunction; however, over-prescription of fluid also appears to impede oxygen delivery and compromise patient outcome. Recent data suggest that early aggressive resuscitation of critically ill patients may limit and/or reverse tissue hypoxia, progression to organ failure, and improve outcome.[5] In a landmark study, Rivers et al. demonstrated that a protocol of early goal-directed therapy reduces organ failure and improves survival in patients with severe sepsis and septic shock.[6] Similarly, a protocol to optimize preload and cardiac output in patients undergoing major surgery reduced postoperative complications and length of stay.[7] Uncorrected hypovolemia, leading to inappropriate infusions of vasopressor agents may increase organ hypoperfusion and ischemia.[8]

However, overzealous fluid resuscitation has been associated with increased complications; increased length of intensive care unit (ICU) and hospital stay, and increased mortality. The first step in the hemodynamic management of critically ill patients is to determine the adequacy of tissue/organ perfusion. Although the signs of shock may be obvious, those of subclinical hypoperfusion may be more subtle (Box 1).

In those patients with indices of inadequate tissue perfusion, fluid resuscitation is generally regarded as the first step in resuscitation. Clinical studies have, however, demonstrated that only approximately 50% of hemodynamically unstable critically ill patients are volume-responsive. The resuscitation of the critically ill patient requires an accurate assessment of the patient's intravascular volume status (cardiac preload) and the likelihood that the patient will respond (increase stroke volume) to a fluid challenge (volume responsiveness).

Box 1: Clinical indices of the adequacy of tissue/organ perfusion.

- Mean arterial pressure—cerebral and abdominal perfusion pressures
- Urine output
- Mentation
- Capillary refill
- Skin perfusion/mottling
- Cold extremities (and cold knees)
- Blood lactate
- Arterial pH, BE and HCO_3
- Mixed venous oxygen saturation ($SmvO_2$) or central venous oxygen saturation ($ScvO_2$)
- Mixed venous pCO_2
- Tissue pCO_2
- Skeletal muscle tissue oxygenation (StO_2)

Fluid challenge has to be given to hypotensive patient presenting either in the emergency, or in clinical scenario in the ICU. How much fluid and how rapidly it is to be administered, and which fluid is to administered is very crucial for a good outcome. Clinical examination may yield important clue to the requirement of fluids, signs of dehydration like diminished skin turgor, thirst, dry mouth, hypernatremia, elevated hematocrit are suggestive of fluid deficit. Circulatory signs of hypovolemia like tachycardia, hypotension, elevated lactate along with signs of decreased renal perfusion like concentrated urine, increased BUN all suggest fluid deficit. A 500 mL of 0.9% saline or balance solutions (plasmalyte) is to be administered over 15–20 minutes; Partial resuscitation using albumin may be considered in hypoalbuminemic patients and in patients with chronic liver disease, heart failure, where large volume crystalloid resuscitation may be very challenging. In the light of present evidence, the use of HES is not recommended in patients with severe sepsis or septic shock.

Fluid challenge may always not be successful. It is effective only in 50% of the cases as various meta-analyses have shown. So the various indices used to predict fluid responsiveness are static and dynamic indices.

Static indices:

- Central venous pressure (CVP)
- Pulmonary artery occlusion pressure (PAOP)

Dynamic indices:

- Passive leg raising (PLR)
- Pulse pressure variation (PPV), or stroke volume variation (SVV)
- *Ultrasonography*: Inferior vena cava (IVC) collapsibility and 2D echocardiogram of the heart chamber.

Central venous pressure has been traditionally used as a guide to fluid therapy. If the CVP is less, then CVP guided fluid challenge can be given as described in Table 4:

Table 4: Fluid challenge: CVP, cm H_2O ("5–2" rule).

Observe CVP for 10 min	<8 cm H_2O	200 mL × 10 min
	<14 cm H_2O	100 mL × 10 min
	>14 cm H_2O	50 mL × 10 min
During infusion 0–9 min	>5 cm	STOP
Following infusion	>2 cm and <5 cm	Wait 10 min
	>2 cm	Wait STOP
	<2 cm	Continue infusion

(CVP: Central venous pressure).

by mansdocs.com

Table 5: Critical components of the fluid challenge—two possible types of response are presented.

	Example 1			*Example 2*		
	Baseline	+10 min	+20 min	Baseline	+10 min	+20 min
1. *Type of fluid*: Normal saline						
2. *Rate of infusion*: 500 mL/30 min						
3. *Clinical end points*: MAP of 65 mm Hg	MAP 50	MAP 60	MAP 65	MAP 50	MAP 60	MAP 60
4. *Pressure safety limit*: CVP of 15 mm Hg	CVP 6	CVP 8 Continue	CVP 12 Stop	CVP 9	CVP 14 Continue	CVP 15 Stop
		Successful fluid challenge			Unsuccessful fluid challenge	

(CVP: Central venous pressure; MAP: Mean arterial pressure).

the "5–2" rule, which was popularized in the 1970s, is still widely used today for guiding fluid therapy. According to this rule, the change in CVP after a fluid challenge is used to guide subsequent fluid management decisions (Table 5).

The CVP is a good approximation of right atrial pressure, which is a major determinant of right ventricular (RV) filling. It has been assumed that the CVP is a good indicator of RV preload. Furthermore, because RV stroke volume (SV) determines left ventricular (LV) filling, the CVP is assumed to be an indirect measure of LV preload. However, due to the changes in venous tone, intrathoracic pressures, LV and RV compliance, and geometry that occur in critically ill patients, there is a poor relationship between the CVP and RV end-diastolic volume. Furthermore, the RV end-diastolic volume may not reflect the patients' position on the Frank-Starling curve and therefore his/her preload reserve.

More than 100 studies have been published to date that have demonstrated no relationship between the CVP (or change in CVP) and fluid responsiveness in various clinical settings.[9,10] Based on this information, we believe that the CVP should no longer be routinely used for guiding fluid management in the ICU, operating room or emergency room.

Until recently, it has been unclear as to which hemodynamically unstable patients are volume-responsive and likely to benefit from fluid resuscitation (fluid boluses). However, during the past decade, a number of dynamic tests of volume responsiveness have been reported. These tests dynamically monitor the change in SV after a maneuver that increases or decreases venous return (preload). These tests allow the clinician to determine the individual patient's position on his/her Frank-Starling curve, and thus determine whether the patient is likely to be fluid-responsive. These techniques use the change in SV during mechanical ventilation or after a PLR maneuver to assess fluid responsiveness.

Spontaneous breathing: During spontaneous breathing systolic blood pressure fluctuates, normally by 5–10 mm Hg also known as "respiratory swing". Pulsus paradoxus is a phenomenon in which the difference in systolic blood pressure between inspiration and expiration is more than 10 mm Hg. Reverse pulsus paradoxus occurs during controlled mechanical ventilation when arterial pressure rises during inspiration and falls during expiration due to changes in intrathoracic pressure secondary to positive pressure ventilation.

Passive Leg Raising

Lifting the legs passively from the horizontal position induces a gravitational transfer of blood from the lower limbs toward the intrathoracic and the volume of blood transferred to the heart during PLR is sufficient to increase the left cardiac preload and thus challenge the Frank-Starling curve. Apart from being easy to use, this method has the advantage of reversing its effects once the legs are tilted down. Therefore, PLR may be considered a reversible "autotransfusion".

The best way to perform a PLR maneuver to predict volume responsiveness is to elevate the lower limbs to 45° (automatic bed elevation or wedge pillow) while at the same time placing the patient in the supine from a 45° semirecumbent position. This induces a larger increase in cardiac preload because it induces the shift of venous blood not only from both the legs but also from the abdominal compartment. The maximal hemodynamic effects of PLR occur within the first minute of leg elevation, it is important to assess these effects by a direct measure of cardiac output or SV (Fig. 3).

by mansdocs.com

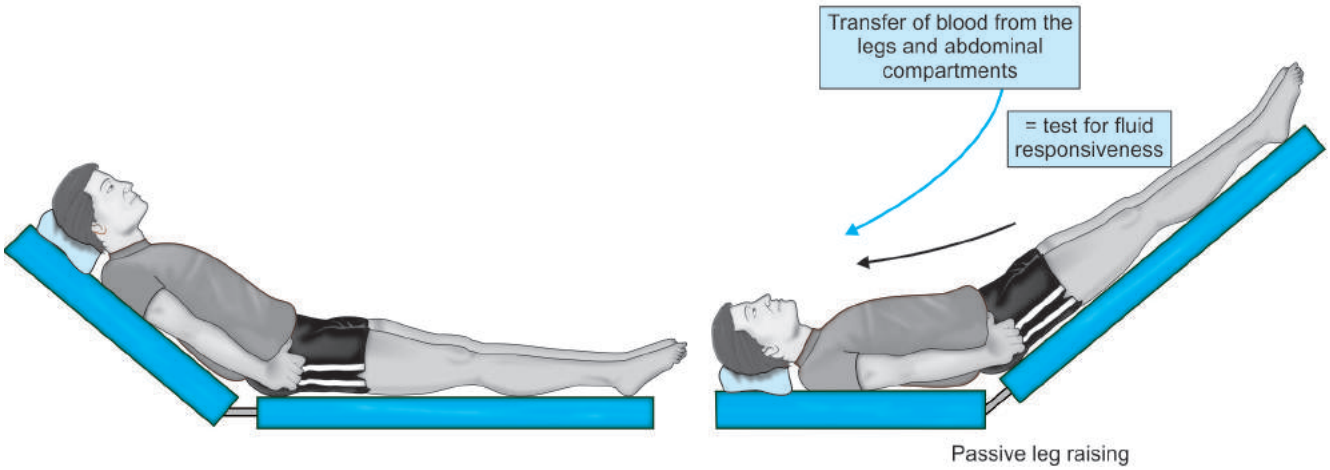


Fig. 3: Passive leg raising. The passive leg raising test consists in measuring the hemodynamic effects of a leg elevation up to 45°. A simple way to perform the postural maneuver is to transfer the patient from the semirecumbent posture to the passive leg raising position by using the automatic motion of the bed.

Stroke Volume Variation or Pulse Pressure Variation

An impressive number of studies have demonstrated that the PPV derived from analysis of the arterial waveform, the SVV derived from pulse contour analysis, and the variation of the amplitude of the pulse oximetry plethysmographic waveform to be highly predictive of fluid responsiveness. A variation of greater than 12–13% has been reported to be highly predictive of volume responsiveness.[11]

Stroke volume variation is a naturally occurring phenomenon in which the arterial pulse pressure falls during inspiration and rises during expiration due to changes in intrathoracic pressure secondary to negative pressure ventilation (spontaneously breathing). Variations over 10 mm Hg have been referred to as pulsus paradoxus. The normal range of variation in spontaneously breathing patients has been reported between 5 mm Hg and 10 mm Hg. Reverse pulsus paradoxus is the same phenomenon with controlled mechanical ventilation, however, in reverse. Arterial pressure rises during inspiration and falls during expiration due to changes in intrathoracic pressure secondary to positive pressure ventilation. In addition to reverse pulsus paradoxus, it has also been referred to as paradoxical pulsus, respiratory paradox, systolic pressure variation and PPV. Traditionally SVV is calculated by taking the $SV_{max} - SV_{min}/SV_{mean}$ over a respiratory cycle or other period of time. SVV and its comparable measurement, PPV, are not indicators of actual preload but of relative preload responsiveness (Fig. 4).

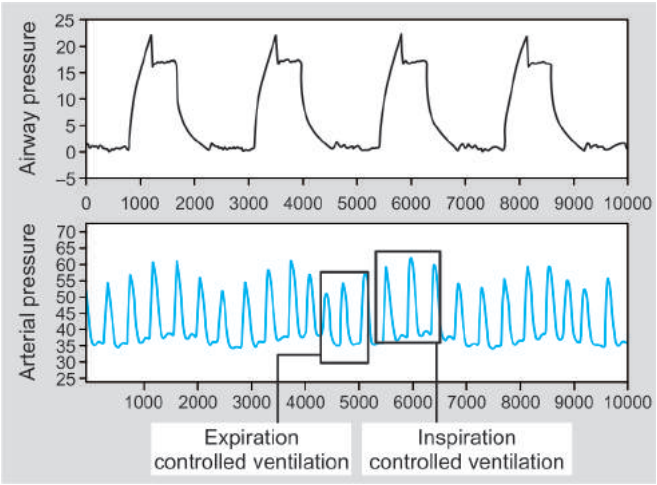


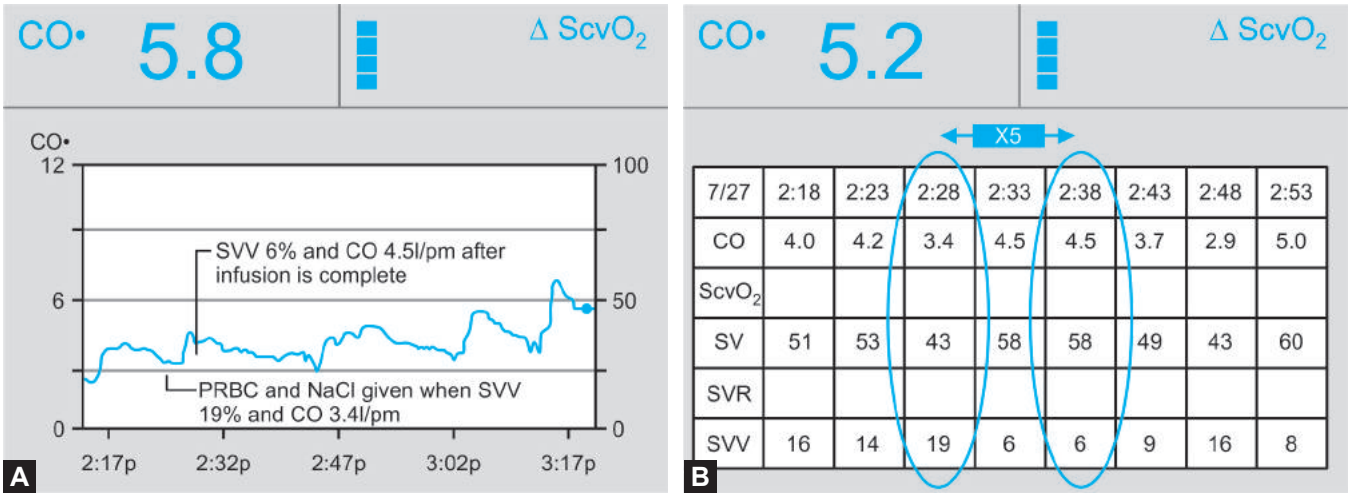
Fig. 4: Pulse pressure variation. The arterial pulse pressure falls during inspiration and rises during expiration.

Normal SVV values are less than 10–15% on controlled mechanical ventilation. Figures 5A and B demonstrate using SVV as a guide for volume resuscitation with a goal SVV of less than 13%. SVV increased to 19% with a SV of 43 mL/beat, blood and saline were given to obtain an SVV of 6% and an SV of 58 mL/beat.

The SVV has got its limitations:

- *Mechanical ventilation*: SVV can be used only on patients who are 100% mechanically (control mode) ventilated with tidal volumes of more than 8cc/kg and fixed respiratory rates.
- *Spontaneous ventilation*: SVV cannot be used on with patients who are spontaneously breathing due to the irregular nature of rate and tidal volumes.

by mansdocs.com



Figs 5A and B: Stroke volume variation.

- *Arrhythmias*: Arrhythmias can dramatically affect SVV values. Thus, the utility of SVV as a guide for volume resuscitation is greatest in absence of arrhythmias.
- *Positive end-expiratory pressure*: Increasing levels of positive end-expiratory pressure may cause an increase in SVV, the effects of which may be corrected by additional volume resuscitation if warranted.
- *Vascular tone*: The effects of vasodilatation therapy may increase SVV and should be considered before treatment with additional volume.

Ultrasound modalities to evaluate preload sensitivity include transthoracic echocardiography, transesophageal echocardiography (TEE), esophageal Doppler and ultrasound of the IVC.

Inferior Vena Cava Diameter Variation

Respiratory change in IVC diameter is an accurate predictor of fluid responsiveness in septic patients.[12] The IVC is a highly compliant vessel with no valves and can be easily distended. The IVC can be identified using either a standard cardiac or abdominal two-dimensional (2D) transducer by a subcostal approach (Fig. 6).[13] Measurements should be made at the hepatic segment of the IVC just cephalad to the origin of the hepatic vein. The IVC is identified with 2D imaging. The respiratory variation in the diameter of the IVC is measured from a frozen M-mode image using the electronic calipers of the machine coincident with ventilator cycling (Fig. 7). Respiratory variation of IVC size in a passive patient on mechanical ventilation in regular heart rhythm has been described as a method of determining volume responsiveness that is easily mastered by the critical care physician.

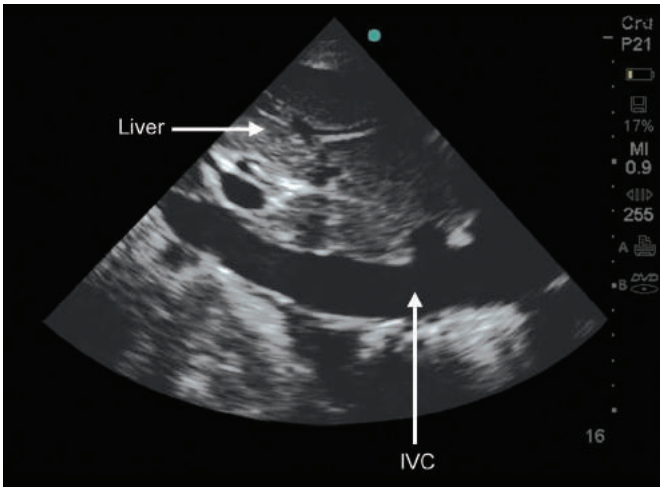


Fig. 6: Longitudinal image of the IVC using a subcoastal view.

A limitation of IVC variation use in determining fluid responsiveness is that the patient must be passive in their interaction with the ventilator. Intra-abdominal hypertension may invalidate this method.

Transthoracic Echocardiography or Transesophageal Echocardiography

One of the major applications of bedside echocardiography is the determination of preload sensitivity.

Ventricular Size

In the patient with shock, the finding of a small hyperdynamic LV with effacement of the end-systolic cavity ("kissing LV walls") strongly suggests major preload sensitivity and is a simple visual clue for immediate volume

by mansdocs.com

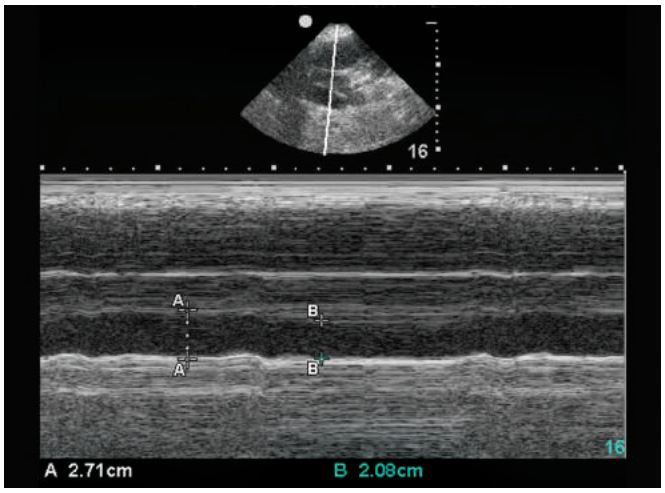


Fig. 7: Measurement of respiratory variation in the diameter of the IVC from a frozen M-mode image. The diameter of the IVC is calculated as [(A – B)/B].

resuscitation of a hypotensive patient. This pattern can be easily identified during goal directed cardiac ultrasound from a parasternal long, short or subcostal view. Cannesson et al.[14] measured changes in LV diastolic area with TEE in the short axis view finding that a 16% variation of LV diastolic area between inspiration and expiration was predictive of preload sensitivity.

CONCLUSION

Fluid balance is an integrated function of various systems working in tandem to maintain an internal milieu, sepsis and septic shock can lead to a gross imbalance in the fluid state of the body. Role of colloids is limited and their use may cause more harm to the patient than benefit, so continued use of colloids is not justified. Fluid challenge and early goal directed therapy is warranted to prevent further damage by septic shock. Fluid challenge responsiveness should be assessed by using various static and dynamic parameters. Dynamic parameters are gaining more and more popularity due to the increased sensitivity in predicting the responsiveness to fluid challenge. IVC collapsibility and echocardiography are tools which can be easily mastered and can give very accurate measurement of preload and response to fluid challenge, so increasing use of new technology is warranted more in emergency room and ICUs.

REFERENCES

1. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247-56.
2. Schierhout G, Roberts I. Fluid resuscitation with colloids or crystalloid solutions in critically ill patients; a systematic review of randomised trials BMJ. 1998;316(7136): 961-4.
3. Albert K, van Vlymen J, James P, et al. Ringer's lactate is compatible with the rapid infusion of AS-3 preserved packed red blood cells. Can J Anaesth. 2009;56(5):352-6.
4. Lamke LO, Liljedahl SO. Plasma volume changes after infusion of various plasma expanders. Resuscitation. 1976;5(2): 93-102.
5. Levy MM, Macias WL, Russell JA, et al. Failure to improve during the first day of therapy is predictive of 28-day mortality in severe sepsis. Chest. 2004;124(Suppl):120 S.
6. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.
7. Lopes MR, Oliveira MA, Pereira VO, et al. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. Crit Care. 2007;11(5):R100.
8. Murakawa K, Kobayashi A. Effects of vasopressors on renal tissue gas tensions during hemorrhagic shock in dogs. Crit Care Med. 1988;16(8):789-92.
9. Michard F, Taboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002; 121(6):2000-8.
10. Marik PE, Baram M, Vahid B. Does the central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134 (1):172-8.
11. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients. A systematic review of the literature. Crit Care Med. 2009;37(9): 2642-7.
12. Barbier C, Loubières Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med. 2004;30(9):1740-6.
13. Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med. 2004;30(9):1834-7.
14. Cannesson M, Slieker J, Desebbe O, et al. Prediction of fluid responsiveness using respiratory variations in left ventricular stroke area by transesophageal echocardiographic automated border detection in mechanically ventilated patients. Crit Care. 2006;10(6):R171.

by mansdocs.com

CHAPTER

5

Vasopressors and Inotropes

Poonam Malhotra Kapoor

INTRODUCTION

Vasopressors and inotropes are a powerful group of drugs that are used in states of shock and tissue hypoperfusion. Vasopressors differ in their action from inotropes. Vasopressors induce vasoconstriction and thus increase the mean arterial pressure (MAP) and therefore the vascular tone, whereas inotropes basically increase the cardiac contractility and thus the cardiac index. Thus, inotropes impact both cardiac function and vascular tone, but vasopressors increase only the vascular tone. However, many drugs have both vasopressor and inotropic effects. These agents are used in critically ill patients with hemodynamic impairment to such an extent that tissue perfusion is insufficient to meet most metabolic demands of the patient. All vasopressors and inotropes are usually administered via a large central vein. In some circumstances, inotropes may be given via a peripheral vein in emergency situations. This chapter dealt with the mechanism of action of commonly used vasopressors and inotropes with a brief review of their pharmacology of these agents used in the intensive care unit (ICU) to treat shock or congestive heart failure (CHF) or inotropic support in postoperative cardiac surgical patient. The last part of the chapter dealt with how to use these agents in evidence-based manner in different cardiac conditions.

MECHANISM OF ACTION OF CATECHOLAMINES

The catecholamines are sympathetic agents which act on receptors of the heart chiefly α and β receptors. The primary catecholamines medications are: epinephrine, norepinephrine, dopamine, dobutamine and neosynephrine. All the adrenergic receptors: α, β and dopamine belong to the G protein receptor (Table 1). These different receptors have different intracellular activities, which are mediated through these G proteins. The β receptors are differentiated into β_1 and β_2 adrenergic receptors. The β_1 stimulation results in enhanced myocardial contractility through Ca^{2+} mediated facilitation of the actin-myosin complex which binds with troponin C and also provides increased chronotropy through this calcium channel activation (Fig. 1A).

Thus, it provides positive chronotropic activation by increasing cyclic adenosine monophosphate (cAMP) levels. This increased cAMP also causes an increase in intracellular vascular Ca^{2+} uptake via the smooth muscle cells through vasodilation and on its action in the sarcoplasmic reticulum via cAMP (Fig. 1B). The stimulation of β_2 adrenergic receptors in blood vessels induces vasodilatation, whereas, β_1 adrenergic receptors are most common in the heart and mediate an increase in inotropy and chronotropy with a minimal vasoconstriction.

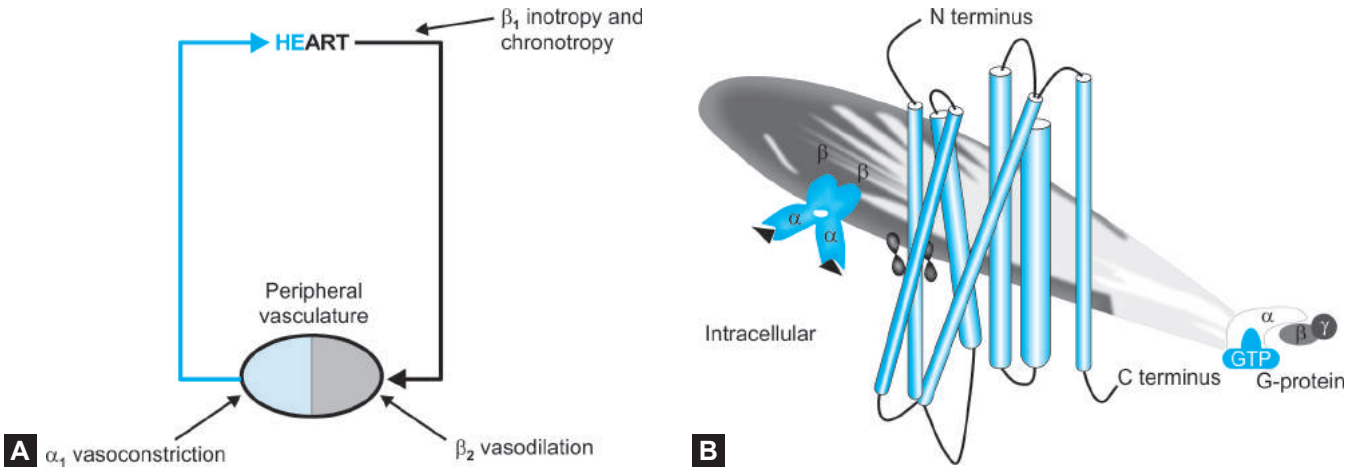
BASIC PRINCIPLES OF USE OF INOTROPES AND VASOPRESSORS

Use of inotropes and vasopressors necessitates care in an intensive care unit or high dependency unit. These vasopressors act on multiple receptors, for instance, multiple effects because of actions upon more than one receptor. For instance, dobutamine increases cardiac output (CO) by β_1 adrenergic receptor activation; however, it also acts

by mansdocs.com

Table 1: Adrenergic receptors and the cardiovascular system.

Receptor	*Location*	*Effect of Stimulation*
α_1 adrenergic	Vascular smooth muscle (peripheral, renal and coronary circulation)	• Vasoconstriction (increasing systemic vascular resistance) • Can increase the duration of contraction without increased chronotropy. However, clinical significance of this phenomenon is unclear
β_1 adrenergic	Heart	• Increased heart rate and increased contractility (increasing cardiac output) • Mediate increases in inotropy and chronotropy with minimal vasoconstriction
β_2 adrenergic	Vascular smooth muscle (peripheral and renal circulation)	• Vasodilatation (reducing systemic vascular resistance) • Stimulation of β_2 adrenergic receptors in blood vessels induces vasodilation



Figs. 1A and B: (A) Locations and effect of stimulation of catecholamine receptor; (B) An adrenergic receptor. Catecholamine binds to the receptor extremely and causes a change the intercellular structure that enables it to activate a G protein.

upon β_2 adrenergic receptors and thus induces vasodilation and can cause hypotension. Many agents have dose-response curves, such that the primary adrenergic receptor subtype activated by the drug is dose-dependent. As an example, dopamine stimulates β_1 adrenergic receptors at doses of 2–10 μg/kg/min, and α-adrenergic receptors when doses exceed 10 μg/kg/min (Table 2). A given agent can affect MAP both by direct actions on adrenergic receptors and by reflex actions triggered by the pharmacologic response. Norepinephrine-induced β_1 adrenergic stimulation alone normally would cause tachycardia. However, the elevated MAP from norepinephrine's α-adrenergic receptor-induced vasoconstriction results in a reflex that decrease in heart rate (HR). The net result may be a stable or slightly reduced HR when the drug is used.

Hypotension

Hypotension may result from hypovolemia, pump failure and pathologic maldistribution of blood flow as in severe sepsis. Vasopressors are indicated for decrease of more than 30 mm Hg per 20% from baseline systolic blood pressure or MAP less than 60 mm Hg and evidence of end-organ dysfunction due to hypoperfusion. Hypovolemia must be corrected first.

Volume Resuscitation

Monitoring the patients fluid balance status is very important during inotropic and vasopressor use. Patients should be adequately fluid resuscitated or fluid therapy should continue with vasopressor use. Using inotropes or vasopressor when patients are fluid depleted can worsen tissue perfusion. Hypotension may result from hypovolemia (e.g. exsanguination), pump failure (e.g. severe medically refractory heart failure or shock complicating myocardial infarction), or a pathologic maldistribution of blood flow (e.g. septic shock, anaphylaxis) (Box 1).

Thus, vasopressors are indicated for a decrease of more than 30 mm Hg from baseline systolic blood pressure, or a MAP less than 60 mm Hg when either condition results in end-organ dysfunction due to hypoperfusion.

by mansdocs.com

Table 2: Receptor actions of different inotropes.

Drug	*Receptor Affinity*	*Action*	*Side Effects*
Noradrenaline	Mainly α_1 agonist, some β_1 agonist action	Vasoconstriction increasing SVR	Reduced renal perfusion as a result of vasoconstriction, increased afterload will reduce SV and increase myocardial oxygen demand (MVO_2)
Adrenaline	*Low dose*: β_1 agonist	Increased heart rate, SV and CO	Tachycardia and tachyarrhythmia, increased MVO_2
	High dose: α_1 agonist	Vasoconstriction at higher dose increasing SVR	High concentrations can cause reduced CO
Dobutamine	β_1 agonist	Increased heart rate, increased CO	Tachyarrhythmia, increased MVO_2
	α_1 agonist	Vasodilatation and reduced SVR	Risk of hypotension
Dopamine	*Low dose*: Dopamine receptor agonist	Vasodilatation of capillary beds, reduced SVR and increased CO	Risk of tachyarrhythmia
	Medium dose: β_1 agonist	Increases contractility, SV and CO	Previously used at low ("renal") doses to maintain renal perfusion and function
	High dose: α_1 agonist	Vasoconstriction increasing afterload, SVR and MAP	No longer used as any benefit on renal outcome is caused by the increased CO

(SVR: Systemic vascular resistance; SV: Stroke volume; CO: Cardiac output; MAP: Mean arterial pressure).

Box 1: Basic principle of vasopressors and inotropes.

The basic principle of a vasopressor/inotrope use always is to correct the hypotension and maintain the cardiac output (CO) and systemic vascular resistance (SVR) as similar, i.e.

MAP = CO × SVR

where, CO = HR × SV

Some of them are mixed action drugs vastly used in states of shock, intraoperative and in the ICU with cardiovascular interventions.

(HR: Heart rate; SV: Stroke volume).

Selection and Titration

Choice of an initial agent should be based upon the suspected underlying etiology of shock (e.g. dobutamine in cases of cardiac failure without significant hypotension). The dose should be titrated to achieve effective blood pressure or end-organ perfusion as evidenced by such criteria as urine output or mentation. If maximal doses of a first agent are inadequate, then a second drug should be added to the first. In situations where this is ineffective, such as refractory septic shock, anecdotal reports describe adding a third agent; although no controlled trials have demonstrated the utility of this approach.

Tachyphylaxis

Responsiveness to these drugs can decrease over time due to tachyphylaxis. Doses must be constantly titrated to adjust for this phenomenon and for changes in the patient's clinical condition.

Hemodynamic Interactions

Mean arterial pressure is influenced by SVR and CO. In situations such as cardiogenic shock, elevating SVR increases afterload and the work of an already failing heart, thus potentially lowering CO. Some authors recommend keeping the SVR approximately 700–1000 dynes x sec/cm^5 to avoid excessive afterload and to minimize complications from profound vasoconstriction. However, there is no consensus regarding an ideal target cardiac index (CI). Studies that have attempted to maintain a supraphysiologic CI of more than 4.0–4.5 L/minute/m^2 have not shown consistent benefit.

Central Line for Infusion is a Must

Catecholamines are given as continuous infusions because of their short half-life. Further, their effects on the cardiovascular system are potent and dosing must be accordingly adjusted for which only an infusion can be used. Thus, it is imperative that inotropes and vasopressors must be always infused via a central vein access because there is a risk of skin necrosis if they extravasate. Invasive monitoring is required because of rapid hemodynamic changes in terms of blood pressure and arrhythmias with these inotropic agents.

Invasive Arterial Pressure Line in the Radial or Femoralartery is a Must

Thus, beat to beat monitoring of arterial pressure via an arterial line becomes mandatory. With these invasive

by mansdocs.com

arterial line, semi or noninvasive CO monitors can be used such as the Flotrac-vigileo/EV-1000 vigileo, LIDCO, PICCO or the esophageal Doppler to simultaneous monitor the CO and SV.

PHYSIOLOGY OF INOTROPES

Inotropes affect the myocyte excitation and contraction at the cellular level. Cardiac muscle fibers contract through the sliding filament mechanism. Actin and myosin filaments are propelled past each other through repeated cross-bridge linking and unlinking. Each cardiac action potential results in the opening of voltage-gated myocyte calcium channels and a rise in intracellular calcium concentration [$(Ca^{2+})i$]. This triggers a further release of calcium from the sarcoplasmic reticulum, which accounts for around three quarters of the total increase in $(Ca^{2+})i$. At rest, tropomyosin blocks the actin-binding site, preventing engagement of myosin heads. Calcium ions bind to troponin C within the troponin complex, displacing tropomyosin. This exposes the actin-binding site, allowing cross-bridge formation with myosin heads. The orientation of the myosin head changes, causing filaments to slide past each other in an adenosine triphosphate (ATP) dependent process. At the end of the action potential, during repolarization, calcium ions are pumped back into the sarcoplasmic reticulum allowing myocardial relaxation (Fig. 2).

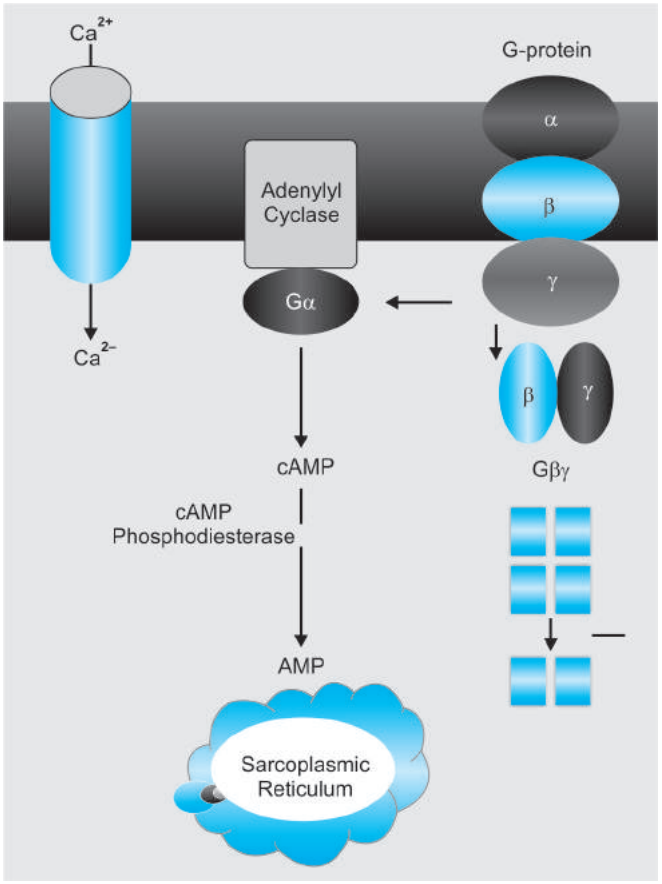


Fig. 2: G protein and cAMP-mediated calcium influx for inotropic action.
(cAMP: Cyclic adenosine monophosphate; AMP: Adenosine monophosphate).

Force and Rate of Myocardial Contraction: Inotropy and Chronotropy

Cardiac output is the volume of blood pumped by the heart each minute and is determined by the force and frequency of ventricular contraction. Increased venous return increases ventricular (and therefore myocyte) stretch in diastole, resulting in increased filament overlap and hence, an increase in the number of available calcium-binding sites. This mechanism, which is the basis of Starling's law of the heart, ensures ventricular output changes in response to changing venous return, thus, ensuring the output of the two ventricles is finely matched. The force of ventricular contraction is also affected by changes in contractility or the force of contraction for a given resting fiber length (Box 2).

Box 2: Physiological factors which determine cardiac output.

Myocyte stretch:
- Changes in venous return
- Changes in plasma volume

Contractility:
- Sympathetic tone
- Circulating catecholamines
- Exogenous inotropes

Heart rate:
- Sympathetic and parasympathetic tone
- Circulating catecholamines
- Exogenous drugs with chronotropic effects

Vascular tone or resistance in vessel tone, sometimes termed afterload, will influence CO both directly and through complex reflexes such as the baroreceptor reflex. For a given preload and contractility, the direct effect of a decrease in afterload is to increase CO and vice-versa as afterload rises. Importantly, during periods of hemodynamic shock, loss of a number of homeostatic mechanisms may impair contractility through acidosis, reductions in

by mansdocs.com

Table 3: Vasoactive medication receptor activity and clinical effects.

	Receptor Activity				
Drug	*Alpha 1*	*Beta 1*	*Beta 2*	*Dopaminergic*	*Predominant Clinical Effects*
Phenylephrine	+++	0	0	0	SVR ↑↑, CO ↔/↑
Norepinephrine	+++	++	0	0	SVR ↑↑, CO ↔/↑
Epinephrine	+++	+++	++	0	CO ↑↑, SVR ↔/↑(high dose)
Dopamine (μg/kg/min)					
0.5–2.0	0	+	0	++	CO, SVR ↑
5.0–10.0	+	++	0	++	CO ↑
10.0–20.0	++	++	0	++	SVR ↑↑
Dobutamine	0/+	+++	++	0	CO ↑, SVR ↓
Isoproterenal	0	+++	+++	0	CO ↑, SVR ↓

(SVR: Systemic vascular resistance; CO: Cardiac output).

coronary flow and an adverse myocardial oxygen supply-demand ratio. Indirect effects of these drugs may also exert complex effects on endothelial permeability and hence, blood volume, which is commonly reduced in critical illness.

PHARMACOLOGY OF INDIVIDUAL AGENTS

Adrenergic agents, such as phenylephrine, norepinephrine, dopamine, and dobutamine, are the most commonly used vasopressor and inotropic drugs in critically ill patients. These agents manifest different receptor selectivity and clinical effects (Table 3).

DRUG CLASSIFICATION OF INOTROPES AND VASOPRESSORS

The inotropes and vasopressors can be broadly classified into the following Table 4.

CATECHOLAMINE VASOPRESSORS AND INOTROPES

Phenylephrine

Phenylephrine (Neosynephrine®) has purely α-adrenergic agonist activity and therefore results in vasoconstriction with minimal inotropy or chronotropy. MAP is augmented by raising SVR. The drug is useful in the setting of hypotension with an SVR less than 700 dynes x sec/cm^5 (e.g. hyperdynamic sepsis, neurologic disorders, anesthesia-induced hypotension).

Although SVR elevation increases cardiac afterload, most studies document that CO is either maintained or actually increased among patients without preexisting cardiac dysfunction. The drug is contraindicated if the SVR is more than 1,200 dynes × sec/cm^5.

Norepinephrine

Norepinephrine (Levophed®) acts on both α_1 and β_1 adrenergic receptors, (Table 5) thus producing potent vasoconstriction as well as a less pronounced increase in CO. A reflex bradycardia usually occurs in response to the increased MAP, such that the mild chronotropic effect is canceled out and the HR remains unchanged or even decreases slightly. Norepinephrine is the drug of choice to treat septic shock wherein its β_1 receptor activity is maximal (Table 3).

Ephedrine

Similar to epinephrine, ephedrine acts primarily on α- and β-adrenergic receptors with less potency. It also has an effect by leading to release of endogenous norepinephrine. Ephedrine is rarely used except in the setting of post-anesthesia-induced hypotension.

Epinephrine

Epinephrine (Adrenalin®) has potent β_1 adrenergic receptor activity and moderate β_2 and α_1 adrenergic receptor effects (Table 5). Clinically, low doses of epinephrine increase CO because of the β_1 adrenergic receptor inotropic and chronotropic effects, while the α-adrenergic receptor-induced vasoconstriction is often offset by the β_2 adrenergic

by mansdocs.com

Table 4: Catecholamine vasopressors and inotropes.

Sympathomimetics	*Other inotropes*
Naturally occurring	cAMP dependent: glucagon
• Epinephrine	cAMP independent
• Norepinephrine	• Vasopressin
• Dopamine	• Terlipressin
Synthetic	• NO synthase inhibitors
• Dobutamine	
• Dopexamine	
• Isoprenaline	

Other Vasopressors Or Non-Catecholamine Vasoactive Drugs

Drug	*Mechanism*	*Action*
Enoximone, milrinone	Phosphodiesterase III (PDE III) inhibitor, prevent hydrolysis of intracellular cyclic AMP, augmenting its effects. Many isoenzymes of phosphodiesterase-PDE III is the target for inotropic actions	Increased cardiac contractility and SV, vasodilatation
Levosimendan	Calcium sensitizor	Increased cardiac contractility without increasing MVO_2, effect on mortality unclear
Vasopressin	Endogenous hormone, also called antidiuretic hormone, V1 receptor activity in vascular smooth muscle increasing intracellular calcium	Vasoconstriction increasing SVR and MAP

(SVR: Systemic vascular resistance; NO: Nitric oxide; CO: Cardiac output; cAMP: Cyclic adenosine monophosphate; AMP: Adenosine monophosphate; MAP: Mean arterial pressure; MVO_2: Myocardial oxygen consumption).

receptor vasodilatation. The result is an increased CO, with decreased SVR and variable effects on the MAP. β_1 adrenergic receptor stimulation may provoke dysrhythmias. The degree of splanchnic vasoconstriction appears to be greater with epinephrine than with equipotent doses of norepinephrine or dopamine in patients with severe shock.

However, the α-adrenergic receptor effect predominates at higher epinephrine doses, producing increased SVR in addition to an increased CO. Epinephrine is most often used for the treatment of anaphylaxis, as a second line agent in septic shock, and for management of hypotension following coronary artery bypass grafting.

Dobutamine

Dobutamine (Dobutrex®) is not a vasopressor but rather is an inotrope that causes vasodilatation. Dobutamine's predominant β_1 adrenergic receptor effect increases inotropy and chronotropy and reduces left ventricular filling pressure. In patients with heart failure this results in a reduction in cardiac sympathetic activity. However, minimal α- and β_2 adrenergic receptor effects result in overall vasodilatation, complemented by reflex vasodilatation to the increased CO. The net effect is increased CO, with decreased SVR with or without a small reduction in blood pressure.

Table 5: Vasopressors and inotropes and their respective receptors.

Vasopressor	*Receptor(s) stimulated*
Norepinephrine	α_1, α_2, β_1
Epinephrine	α_1, α_2, β_1, β_2
Dopamine	Dopaminergic α_2, β_1
Phenylephrine	α_1, α_2
Metaraminol	α_1, β_1
Ephedrine	α_1, β_1, β_2
Vasopressin	V-1, V-2
Dobutamine	α_1, β_1, β_2

Dobutamine is most frequently used in severe, medically refractory heart failure and cardiogenic shock and in severe sepsis as recommended by surviving sepsis guidelines.

Dopamine

Dopamine (Intropin®) has a variety of effects depending upon the dose range administered:

- At doses of 1–2 **μg/kg/min, dopamine acts predominantly** on dopamine-1 receptors in the renal, mesenteric, cerebral, and coronary beds, resulting in selective vasodilatation. Some reports suggest that dopamine increases urine output by augmenting renal blood flow and glomerular filtration rate, and natriuresis by

by mansdocs.com

inhibiting aldosterone and renal tubular sodium transport. These effects may be blunted by haloperidol and other butyrophenones. However, the clinical significance of these phenomena is unclear, and some patients may develop hypotension at these low doses.

- At 5–10 μg/kg/min, dopamine also stimulates β_1 adrenergic receptors and increases CO, predominantly by increasing SV with variable effects on HR. Doses between 2 μg/kg/min and 5 μg/kg/min have variable effects on hemodynamics in individual patients: vasodilation is often balanced by increased SV, producing little net effect upon MAP. Some mild α-adrenergic receptor activation increases SVR, and the sum of these effects is an increase in MAP.
- At doses more than 10 μg/kg/min, the predominant effect of dopamine is to stimulate α-adrenergic receptors and produce vasoconstriction with an increased SVR. However, the overall α-adrenergic receptor effect of dopamine is weaker than that of norepinephrine, and the β_1 adrenergic receptor stimulation of dopamine at doses more than 2 μg/kg/min can result in dose-limiting dysrhythmias.

In practical terms, the dose-dependent effects of dopamine mean that increasing the dose of the drug is akin to switching vasopressors. Conversely, simply increasing the dose of dopamine without being cognizant of the different receptor populations activated can cause untoward results.

The usual dose range for dopamine is 2–20 μg/kg/min, although doses as high as 130 μg/kg/min have been employed. Dopamine is most often used in hypotension due to sepsis or cardiac failure, where it should be started at 2 μg/kg/min and then titrated to a desired physiologic effect rather than a predicted pharmacologic range. Such titration is necessary because weight-based administration of dopamine can achieve quite different serum drug concentrations in different individuals. It has been shown to increase mortality in cardiogenic/sepsis shock probably by increasing the incidence of arrhythmias.

Isoproterenol

Isoproterenol (Isuprel®) also is primarily an inotropic and chronotropic agent rather than a vasopressor. It acts upon β_1 adrenergic receptors and, unlike dobutamine, has a prominent chronotropic effect. The drug's high affinity for the β_2 adrenergic receptor causes vasodilatation and a decrease in MAP. Therefore, its utility in hypotensive patients is limited to situations in which hypotension results from bradycardia, e.g. complete heart block while awaiting pacemaker.

Noncatecholamine Vasopressors and Inotropes

A number of agents produce vasoconstriction or inotropy through nonadrenergic mechanisms, including phosphodiesterase inhibitors (PDIs), and nitric oxide synthase inhibitors.

Vasopressin

Vasopressin is an antidiuretic hormone (ADH) analogue usually used in the management of diabetes insipidus and esophageal variceal bleeding, but nonrandomized, open label case series have suggested that it also may be useful in the treatment of refractory septic shock, particularly as a second pressor agent.

Although vasopressin is a weak pressor in normal subjects, a small randomized controlled clinical trial found that the addition of vasopressin (infused at a fixed rate of 0.04 U/min) to norepinephrine was more effective in reversing late vasodilatory shock than norepinephrine alone. Similar results were noted when norepinephrine and vasopressin were compared in a blinded study of 23 patients with severe septic shock. The use of vasopressin was associated with a decreased requirement for other vasopressors, higher urine output, and improved creatinine clearance. Vasopressin may be used instead of the second close of epinephrine in advanced cardiac life support (ACLS).

Terlipressin

Terlipressin, an ADH analogue with a serum half-life of 6 hours is used in the management of variceal hemorrhage and in patients with sepsis. In several small open label trials, terlipressin has been reported to improve the hemodynamic profile and decrease (or eliminate) the requirement for catecholamine vasopressors in patients with sepsis. However, randomized clinical trials demonstrating a clear benefit are lacking, and rebound hypotension appears to be common following withdrawal. In addition, terlipressin is not available for clinical use in the United States.

The precise role of vasopressin and terlipressin for the treatment of vasodilatory shock remains to be defined. Potential complications of ADH analogue in this setting include coronary and mesenteric ischemia, hyponatremia, pulmonary vasoconstriction, and skin necrosis from peripheral infusion.

by mansdocs.com

PHOSPHODIESTERASE INHIBITORS

Phosphodiesterase inhibitors, such as amrinone and milrinone, are nonadrenergic drugs with inotropic and vasodilatory actions. In many ways, their effects are similar to those of dobutamine but with a lower incidence of dysrhythmias. PDIs most often are used to treat patients with impaired cardiac function and medically refractory heart failure, particularly right heart failure but their vasodilatory properties limit their use in hypotensive patients, although addition of norepinephrine may ameliorate this effect.

Milrinone

Milrinone is a type III PDI that prevents cAMP degradation, leading to a potentiation of β-receptor effects in cardiac and vascular smooth muscle. It has been shown to overcome 1 and 2 receptor down-regulation and has been recommended for nitrovasodilator resistant low cardiac output syndrome (LCOS) in sepsis. Recently, the PRIMACORP study demonstrated the safety and efficacy of milrinone in preventing LCOS in infants and children after corrective surgery for congenital heart disease.

NEWER AGENTS

Nitric Oxide Synthase Inhibitors

Nitric oxide overproduction appears to play a major role in vasodilatation induced by sepsis. Studies of nitric oxide synthase inhibitors such as N-monomethyl-L-arginine (L-NMMA) in sepsis demonstrate a dose-dependent increase in SVR. However, CI and HR decrease, even when patients are treated concomitantly with norepinephrine or epinephrine. The increase in SVR tends to be offset by the decrease in CI, such that MAP is only minimally augmented. The clinical utility of this class of drugs remains unproven.

Levosimendan

Levosimendan is a new myocardial myofilament calcium sensitizer that binds to troponin C, stabilizing the calcium induced change in conformation and enhancing contractility. There also appears to be ATP-dependent potassium channel induced peripheral and coronary vasodilation and, perhaps, phosphodiesterase III inhibition at high doses. It has inotropic and lusitropic actions in failing human myocardium with the inotropic effect dominating at low dose. The active metabolite (OR-1896) has a prolonged half-life providing sustained benefit. Significant survival benefit was demonstrated in two large adult trials.

Tezosentan

Tezosentan is another recently introduced compound that has actions as an endothelin antagonist. The endothelin receptors mediate vasoconstriction (via ETA and ETB2) and vasodilation (via ETB1). Tezosentan has 30 times the affinity for ETA, functioning as a potent vasodilator at low doses. Its pharmacokinetics renders it suitable for infusion and it has been used successfully in humans with congestive cardiac failure. It has been shown to improve cardiac performance in septic shock at low doses (with reductions in SVR and PVR in pigs) whilst ETB1 mediated vasoconstriction appears to predominate with dose escalation.

CLINICAL EVIDENCE OF INOTROPES AND VASOPRESSOR USE IN DIFFERENT CLINICAL STUDY

Dosing and Administration in Different Clinical Trials

Reported doses of sympathomimetic amines vary greatly in various clinical trials. Doses of norepinephrine and phenylephrine for septic shock are generally higher than those reported in textbooks or product labeling. Table 6 summarizes the dosing used at our institution. Milrinone may be initiated with a bolus dose of 50 **μg/kg intrave**nously over 10 minutes followed by a continuous infusion of 0.5 μg/kg/min for patients with creatinine clearance of more than 50 mL/min/m^2. The infusion can be adjusted from 0.375 μg/kg/min to 0.75 μg/kg/min. Adjustments for renal insufficiency is summarized. For septic shock, the Surviving Sepsis Guidelines recommend that vasopressin be given at a continuous infusion of 0.01–0.04 μg/min. It is *not titrated*, and this dose should not be exceeded to limit adverse reactions (Table 6).

Although some areas in the treatment of critically ill patients with shock remain controversial such as the best vasopressor or combination of vasopressors to use, and what the optimal hemodynamic goals are, several conclusions can be drawn from the published literature:

- The traditional approach of awaiting ICU admission and inserting a pulmonary artery catheter without having a protocolized treatment does not improve morbidity or mortality of critically ill patients and patients with shock.

by mansdocs.com

Table 6: Recommended infusion rate of milrinone based on renal function.

CrCl, mL/min/1.73 m²	*Rate, µg/kg/min*
5	0.2
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43
>50	0.5

- Early optimization begun in the emergency department does improve morbidity and mortality.
- A standardized or protocolized treatment approach such as the Surviving Sepsis Guidelines will improve morbidity and mortality.

INOTROPES FOR CARDIOGENIC SHOCK, CONGESTIVE HEART FAILURE AND POSTOPERATIVE SUPPORT

The catecholamines with mixed α and β effects such as dopamine and epinephrine and the pure inotropes such as dobutamine and milrinone have been used for many years for the treatment of heart failure (following myocardial infarction or acute exacerbations of CHF) and for supporting CI after procedures such as coronary artery bypass grafting and valve replacement surgery. In the treatment of cardiogenic shock, agents with combined α, β are frequently initially used to increase both CI and MAP. When MAP is adequate, pure inotropes such as dobutamine and milrinone are frequently used for treating heart failure or for postoperative CI support. When pure inotropes are used, a combination of a vasopressor such as norepinephrine can be utilized, if necessary, to maintain MAP. However, vasopressors should be titrated carefully as the increase in afterload can decrease CI. Very few large-scale randomized trials compare inotropes in the setting of heart failure or postprocedure support. The small trials that are published compare only hemodynamic effects and effects on HR, arrhythmias, and myocardial oxygen balance. The results of comparative trials between dobutamine and the inodilators or milrinone can be summarized as follows:

- Inodilators generally have a greater effect on decreasing pulmonary capillary wedge pressure (PCWP) and SVR than dobutamine, but have an equal effect on increasing the CI.
- Studies generally show that the PDIs have the same or less effect on increasing HR.
- Inotropes have no effect on MVO_2, whereas dobutamine generally increases it. However, dobutamine also increases myocardial oxygen delivery, which counterbalances the effect on consumption.
- There have been no clinically significant differences demonstrated between the inodilators and dobutamine in terms of inducing myocardial ischemia.
- One theoretical advantage of inodilators is that they do not have the issue of tolerance (declining efficacy) over time as compared to dobutamine. Tolerance to dobutamine does occur in 48–72 hours. However, inotropic support should be a short-term treatment until more definitive therapy or mechanical support (e.g. ventricular assist device) can be provided as long-term treatment with inotropes has been associated with increased mortality.
- A potential disadvantage is the long half-life of the Inodilators as compared with that of dobutamine as adverse reactions such as tachyarrhythmias may take longer to dissipate with the PDIs after discontinuation.
- Several studies have shown that Inotropes can have additive effects when combined with dobutamine. Therefore, inodilators and dobutamine may be used in combination when an adequate CI cannot be obtained with either agent alone.

Anemia and Vasopressors Use

In an article entitled "immediate postoperative hemoglobin in cardiovascular surgery as predictor of vasopressors and inotropes in the ICU by Mabel Goinez et al. The latter while studying the role of low hemoglobin in the immediate postoperative period as an independent marker for the need of hemodynamic support, concluded that while undergoing CV surgery about 82% had no postoperative anemia (i.e. Hb was >9 g/dL) of the remaining patients whose Hb was less than 9 g/dL (i.e. they were anemic, about 62% required vasopressors and about 41% required inotropes during their stay in the ICU, thus making hemoglobin as a strong predictor.

CLINICAL USES HEMODYNAMIC GOALS IN SEPTIC SHOCK AND ACUTE RESPIRATORY DISTRESS SYNDROME

Two main hemodynamic goals are as follows:

1. Provide an adequate perfusion pressure that will ensure blood flow to vital organs and
2. Provide an adequate level of oxygen delivery.

by mansdocs.com

Table 7: Level of evidence according to the surviving sepsis guidelines.

S. No	Guidelines	Level of evidence	Comments
1.	Either noradrenaline or dopamine is the first-line choice of vasopressor to correct hypotension in septic shock	Level II	There is no high-quality evidence to recommend one catecholamine over another, but recommended using noradrenaline or dopamine over adrenaline or dopamine over adrenaline primarily because of the risk of splanchnic ischemia associated with the latter. This is an unfounded concern based on poor quality studies that used non-validated measurement and overstates the risks.
2.	Low-dose dopamine should not be used for renal protection as part of treatment of severe sepsis	Level I	This trial was the Australian and New Zealand Intensive Care Society Clinical Trial Group Dopamine study, which has definitively answered the question
3.	Vasopressin may be considered in patients with refractory shock despite high-dose conventional vasopressors	Level IV–V	This is the correct level of evidence for this recommendation. Vasopressin should be reserved for patients with catecholamine-resistant septic shock, although the threshold for its use remains elusive
4.	Dobutamine may be used to increase cardiac output in patients with low cardiac output, and may be combined with vasopressor therapy in the presence of low blood pressure		Dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of left ventricular filling (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure
5.	A strategy of increasing cardiac index to achieve an arbitrarily defined elevated level is not recommended	Level I	The guideline authors refer to two negative trials of dobutamine to induce supranormal oxygen delivery in sepsis

The American College of Critical Care Medicine (ACCM) has published guidelines for hemodynamic support of adult patients with septic shock. In terms of perfusion pressure; the general guideline (mostly from animal models) is that a MAP of 60–65 mm Hg is generally needed to perfuse organs. One clinical trial demonstrated that achieving a higher MAP of 75 or 85 mm Hg did not have any benefit in terms of blood flow, urine output, or splanchnic perfusion. Therefore, a MAP of 60–65 mm Hg appears to be a reasonable goal.

In terms of optimizing oxygen delivery, the goals are less clear. Studies have suggested that patients with critical illness (both surgical and septic shock patients) have better outcomes in terms of morbidity and mortality if they have higher than normal levels of oxygen delivery and consumption [defined as CI >4.5 L/min, oxygen delivery (DO_2) of >600 mL/min/m2, and oxygen consumption (VO_2) >170 mL/min/m^2]. However, multicenter prospective evaluations of treating patients to these "hyperdynamic" levels of oxygen delivery and consumption have not shown a consistent benefit, and one trial showed a detrimental effect on mortality when utilizing high doses of dobutamine to achieve these goals. Part of the issue may be the timing of interventions to achieve optimal goals. Rivers et al conducted a prospective randomized trial assessing early goal directed (EGD) therapy in the treatment of severe sepsis and septic shock used dobutamine if the perfusion remained low despite other measures.

Level of Evidence According to the Surviving Sepsis Guidelines

Level of evidence according to the surviving sepsis guidelines are given below in Table 7.

CONCLUSION

Inotropic therapy has been furnished with some new understanding of older agents and new ways of using them. Some agents are gaining an evidence base, whilst even newer agents need such a base. Guidelines are emerging to facilitate their use.

Once an adequate perfusion pressure has been established in septic shock, the next goal to assess is whether or not oxygen delivery to tissues is adequate. As previously discussed, what defines an adequate level of delivery is controversial. Oxygen delivery is optimized by evaluating the components that determine oxygen delivery: arterial oxygen saturation, hemoglobin, and CI. Inotropes can be used to increase oxygen delivery by increasing CI. However, because they may also cause vasodilatation, they may need to be utilized in combination with vasoconstrictors to maintain blood pressure. Dobutamine is the inotrope that has been the most widely studied in septic shock. In the study of EGD by Rivers et al. dobutamine was used to increase oxygen delivery when it was inadequate as determined by a low central venous saturation. The ACCM guidelines recommend that dobutamine be used as the

by mansdocs.com

first choice for septic shock patients with low CI and/or low venous saturation and an adequate MAP following fluid resuscitation. Dobutamine may also be useful in patients with evidence of tissue hypoperfusion (such as low urine output or elevated lactic acid). However, strategies to routinely increase CI to "supranormal" values (CI >4.5 L/min/m^2) has not been shown to improve outcome. An important point that is stressed in published guidelines is that vasopressors and inotropes *should be titrated separately* to different goals. Vasopressors are titrated to maintain an adequate MAP while inotropes are titrated to the desired effect on oxygen delivery (e.g. desired CI or central venous saturation >70%).

It seems intuitive to use the predominant naturally occurring catecholamines, noradrenaline or adrenaline as the first line agent(s) for circulatory failure. Supplemental endocrine replacement therapy with low-dose corticosteroids and vasopressin appears to have an emerging role in this strategy, but requires circumspection. The results of large-scale, high quality trials of endogenous catecholamines for sepsis, septic shock and cardiac ICU setting provide additional important information for evidence-based guidelines, which remain of limited clinical utility.

BIBLIOGRAPHY

1. Bangash MN, Kong ML, Pearse RM, et. al. Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol. 2012;165:2015-33.
2. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32:858-73.
3. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med. 2010;36:83-91.
4. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004;32:1928-48.
5. LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med. 2000;28:2729-32.
6. Martikainen TJ, Tenhunen JJ, Uusaro A, et al. The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock. Anesth Analg. 2003;97:1756-63.
7. Micek ST, Roubinian N, Heuring T, et al. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med. 2006;34:2707-13.
8. Muller S, How OJ, Hermansen SE, et al. Vasopressin impairs brain, heart and kidney perfusion: an experimental study in pigs after transient myocardial ischemia. Crit Care. 2010;12:R20.
9. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med. 2007;35:1105-12.
10. Overgaard CB, Dzavík V inotropes and vasopressors review of physiology and clinical uses in cardiovascular disease. Circulation. 2008;118:1047-56.
11. Rivers E, Nguyen B, Havstad S, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.
12. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877-87.
13. Russell JA, Walley KR. Vasopressin and its immune effects in septic shock. J Innate Immun. 2010;2:446-60.
14. Simon F, Giudici R, Scheuerle A, et al. Comparison of cardiac, hepatic, and renal effects of arginine vasopressin and noradrenaline during porcine fecal peritonitis: a randomized controlled trial. Crit Care. 2009;13:R113.
15. Westphal M, Freise H, Kehrel BE, et al. Arginine vasopressin compromises gut mucosal microcirculation in septic rats. Crit Care Med. 2004;32:194-200.

by mansdocs.com

CHAPTER

6

Multiple Organ Dysfunction Syndrome

R Pratheema, R Senthilkumar, N Ramakrishnan

INTRODUCTION

In the past two decades, advances in resuscitation and life support in critical illness has increased the prevalence of multiple organ dysfunction syndrome (MODS). It is a disease of medical progress. The characteristic feature of MODS is that the morbidity and mortality of the patients are due to the pathophysiological consequences (sequential dysfunction and failure of several organ systems) of the illness rather than the presenting illness itself.

DEFINITION

Multiple organ dysfunction system is "the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention". It is a condition of continuously changing organ function finally organ failure.

MECHANISMS OF MULTIPLE ORGAN DYSFUNCTION SYNDROME

The progressive dysfunction of organ systems that characterize MODS usually occurs in a predictable manner. During the first 72 hours of the original insult, respiratory failure commonly occurs. This is followed by hepatic failure (5–7 days), gastrointestinal bleeding (10–15 days), and finally renal failure (11–17 days). The pathological processes leading to MODS have not been well defined. There are, however, several hypotheses as to the mechanisms that initiate and perpetuate MODS.

PATHOGENESIS

Multiple organ dysfunction syndrome results from the inflammatory and anti-inflammatory processes in the host (Fig. 1 and Table 1). A diffuse generalized inflammatory response of the host occurs in response to a variety of stimuli including infectious (bacteria, fungi, viruses, parasites and toxins) or noninfectious stimuli (pancreatitis, trauma, burns, hemorrhage, blood transfusion and others). This systemic inflammatory response syndrome (SIRS) attempts to protect the host against the effects of the injurious stimuli. However, when the response is severe, it may injure the host by overwhelming its normal protective mechanisms.

Systemic inflammatory response syndrome causes activation of endothelium and macrophages, liberating cytokines, releasing oxygen-free radicals and nitric oxide (NO), which leads to further inflammatory damage. When severe, this may induce hypotension, hypoperfusion (Fig. 2) and organ dysfunction which are clinically manifested as altered mental status, oliguria, cold extremities and laboratory evidence of lactic acidosis.

Clinically, SIRS is diagnosed by the presence of two or more of criteria including:

- Body temperature (> 38°C or < 36°C)
- Heart rate (HR) [> 90 beats/minutes (bpm)]
- Respiratory rate higher than 20 breaths/minutes (bpm) or arterial carbon dioxide tension ($PaCO_2$) below 32 mm Hg
- White blood cell (WBC) count higher than 12,000 cells/mm^3 or lower than 4,000 cells/mm^3 or presence of more than 10% of immature forms.

by mansdocs.com

Table 1: Factors related to patient, injury and treatment .

Patient factors	*Injury factors*	*Treatment factors*
• Age >55 years	• Injury severity	• Duration and depth of shock
• Male gender	• Blunt trauma	• Units of red blood cells (RBC) and its age
• Body mass index	• Contaminated wound	• Mechanical ventilation
• Medical comorbidities	• Time to retrieval	• Surgery and long bone fixation
• Genetic	• Organ ischemic/reperfusion	• Abdominal compartment syndrome

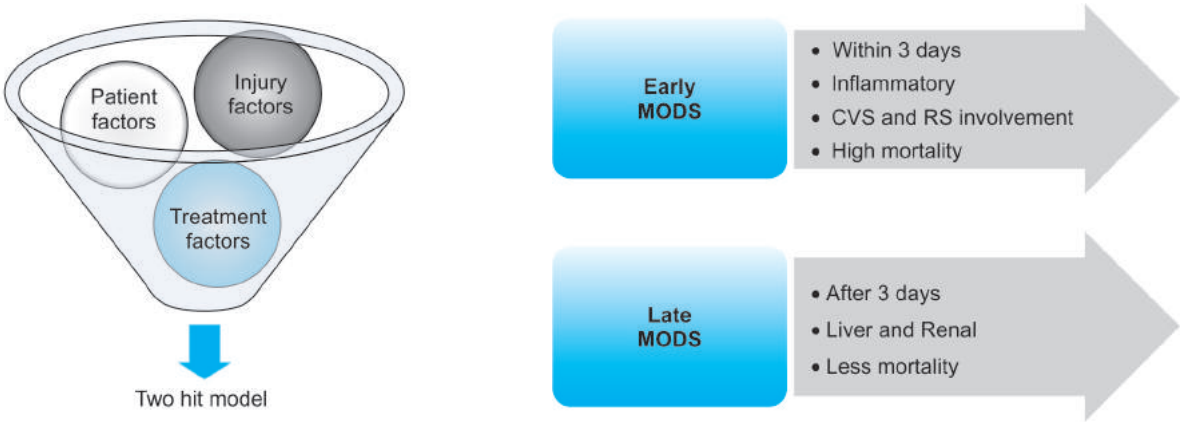


Fig. 1: Pathogenesis of multiple organ dysfunction syndrome.
(CVS: Cardiovascular system; MODS: Multiple organ dysfunction syndrome; RS: Respiratory system).

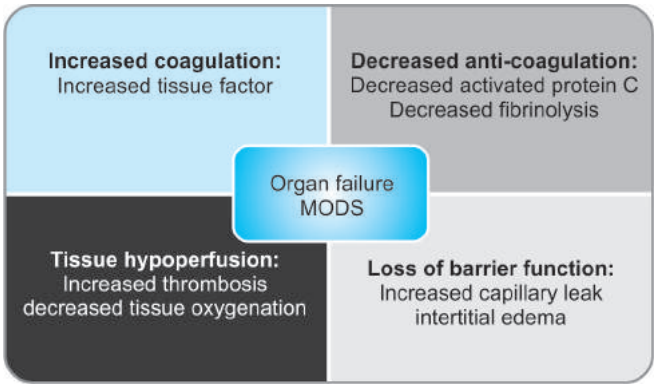


Fig. 2: Components of multiple organ dysfunction syndrome (MODS).

The clinician should always appreciate that the body has balancing mechanisms and that any disturbance of these balances induce discomfort, injury or disease. The aim of the astute clinician would be to cautiously return the balances early in the clinical course.

A stimulus may cause SIRS with its mediators that are proinflammatory [cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6 and IL-8] along with activation of coagulation and complement cascade. The second phase response then initiates an anti-inflammatory response with cytokines, such as IL-4, IL-8, IL-10 and prostaglandin E_2 (PGE_2), to counteract and balance the ongoing inflammation with the same stimuli. This is the compensatory anti-inflammatory response syndrome (CARS).

If SIRS predominates, the patient may suffer from MODS and if CARS predominates, the balance would help with the recovery process. When infection is the underlying cause of SIRS, the condition is called sepsis. When sepsis is accompanied by hypotension that responds to volume loading or by dysfunction of one or more organ, it is referred to as severe sepsis. When severe sepsis is accompanied by hypotension that is refractory to volume loading and needs vasopressor support, the condition is called septic shock.

GUT HYPOTHESIS

The gut hypothesis is currently the most popular theory to explain the development of MODS in critically ill patients. Splanchnic hypoperfusion is a common phenomenon

by mansdocs.com

following trauma, sepsis, shock, or thermal injuries. Along with this, endotoxins cause a dose-dependent reduction in the diameter of the central arteriole of the villus. The high susceptibility of the gut to diminished tissue perfusion and oxygenation due to its critical oxygen requirement being higher than other vital organs, along with mucosal countercurrent microcirculation renders the villi, particularly vulnerable to ischemia. Mucosal ischemia leads to both structural changes and alterations in cellular function. Endotoxins also cause mucosal injury by generating reactive oxygen species and inhibiting mitochondrial respiration in enterocytes. The gut mucosal injury increases gut permeability, alters gut immune function, and causes translocation of bacteria. Due to hepatic dysfunction, these bacterial toxins escape into the systemic circulation and activate the hosts' inflammatory response, leading to tissue injury and organ dysfunction.

A number of clinical studies support the gut hypothesis. Doig et al. showed an excellent relationship comparing increased intestinal permeability on admission of patient to the intensive care unit (ICU) and the subsequent development of MODS. O'Boyle et al. examined and reported the mesenteric lymph nodes, serosal scrapings and peripheral blood of a large group of patients undergoing laparotomy. Bacterial translocation was present in 15% of patients, and these patients had a significantly greater risk of developing septic complications and MODS. In a group of septic patients, Marik demonstrated that a low gastric intramucosal pH (pHi) was associated with the development of MODS. Further, studies have demonstrated that the failure of splanchnic resuscitation to normalize the pHi in acutely injured trauma patients was associated with increased incidence of MODS. Low pHi during the intraoperative period in a group of patients undergoing major surgery has also been shown to be associated with the development of MODS.

Endotoxin-Macrophage Hypothesis

Endotoxin has been proposed as a key mediator in MODS as primary or secondary infection with *Gram-negative* microorganisms is common in this group of patients. As per this hypothesis, after the initial event (stimuli, i.e. sepsis, trauma), MODS develops as a result of production and liberation of cytokines and other mediators by macrophages which are endotoxin-activated. TNF-α, IL-1, IL-6, thromboxane α2, prostacyclin, platelet-activating factor and NO are the proinflammatory mediators that may be involved in the development of MODS.

Tissue Hypoxia-Microvascular Hypothesis

As a consequence of macro- and microvascular changes, cellular oxygen supply may become inadequate. Anemia, hypoxemia, protracted hypovolemia and myocardial failure will result in a decrease in tissue oxygen delivery. In addition, sepsis is characterized by an imbalance of hemostasis with widespread microvascular thrombosis, which has been strongly implicated in the development of organ failure. Tissue hypoxia may result in organ dysfunction and eventually cell death.

The Two-Event Hypothesis

This hypothesis proposes that an injury primes the innate immune system and at a later time, a secondary insult during a vulnerable window provokes unbridled systemic inflammation that results in MODS.

Integrated Hypothesis

In most patients with MODS, this syndrome cannot be traced to a single cause. It is likely that MODS is the end result of dysregulated hemostasis involving most of the mechanisms cited above.

Multiple organ dysfunction syndrome is a progressive process, and this model of clinical staging (Table 2) is arbitrary and attempts to describe evolution of organ dysfunction.

Scoring: It includes six parameters to assess the severity of organ dysfunction with a maximum of 24 points (Table 3). When applied to critically ill ICU patients, mortality was approximately:

- 25% when the score was 9–12 points
- 50% with a score of 13–16 points

Table 2: Clinical staging.

Stage 1	• Patient appears normal. • Upon close evaluation, it is clear that his volume requirements are a little higher than expected. • Mild laboratory abnormalities may provide a clue suggesting early organ dysfunction.
Stage 2	• Patient appears ill. • Occult organ dysfunction • Unfortunately, treatment may start only at this stage which may be somewhat late.
Stage 3	• Overt organ dysfunction requiring support. • Starting treatment at this stage is very late.
Stage 4	• Sequential organ failure • Increased mortality if identified only at this stage

by mansdocs.com

Table 3: The multiple organ dysfunction syndrome (MODS) score.

		Points				
Parameters		*0*	*1*	*2*	*3*	*4*
PaO_2/FiO_2		> 300	226–300	151–225	76–150	≤ 75
Serum creatinine	µmol/L	≤ 100	101–200	201–350	351–500	> 500
	mg/dL	≤ 1.2	1.2–2.26	2.27–3.96	3.97–5.66	> 5.66
Serum bilirubin	µmol/L	≤ 20	21–60	61–120	121–240	> 240
	mg/dL	≤ 1.2	1.21–3.5	3.51–7	7.01–14	> 14
PAR*		≤ 10	10.1–15	15.1–20	20.1–30	> 30
Platelet count (1,000/mm^3)		> 120	81–120	51–80	21–50	≤ 20
Glasgow Coma score**		15	13–14	10–12	7–9	≤ 6

*PAR = HR × (CVP/MAP).

**The best estimate in the absence of sedation.

(CVP: Central venous pressure; FiO_2: Fraction of inspired oxygen; HR: Heart rate; MAP: Mean arterial pressure; PaO_2: Partial pressure of oxygen in arterial blood; PAR: Pressure-adjusted heart rate).

- 75% with a score of 17–20 points
- 100% with a score greater than 20 points.

Other severity of illness scoring systems, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Mortality Probability Model (MPM) and Organ Failure Index (OFI), have been used to estimate the probability of hospital mortality. Inflammatory markers have been also used for assessment of organ dysfunctions, including acute phase proteins, cytokines, complement and coagulation factors and other surrogate nonspecific markers as albumin, cholesterol and transferrin. Although several scoring systems and markers have been proposed, the tissue perfusion and oxygenation parameters may be the most useful from a clinical standpoint. However, it should be noted that there are no gold standards for this purpose and a combination of parameters and close clinical monitoring are important while managing patients with MODS.

MANAGEMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME/MULTIPLE ORGAN FAILURE

The current management of patients with MODS/multiple organ failure (MOF) is predominantly supportive. The objective is directed at identifying and treating the underlying disorder. The common predisposing conditions for the development of MODS/MOF are infection and sepsis, and it is important to investigate for the presence of active infection. Frequently, it may be necessary to use sophisticated imaging techniques and other diagnostic studies in addition to obtaining adequate culture specimens from potential infective sources. Early administration of appropriate, effective antibiotic therapy has been shown to be beneficial in the management (Table 4).

More importance should be given to prevent MODS/MOF in the critically ill patient as its onset has a dramatic effect on morbidity and mortality. Basic organ support measures provided for all critically ill patients could prevent development and/or worsening of MODS.

Pulmonary management is directed at supporting oxygenation and ventilation. The value of early intubation and mechanical ventilatory support to improve the blood flow to the diaphragm and accessory muscles of respiration has been recommended by most clinicians. The decision regarding early intubation and ventilatory support needs to be weighed against the potential complications associated with the procedure.

There is no debate on the importance of ensuring an adequate amount of tissue oxygen delivery. Unfortunately, the definition of adequate has been a topic of debate and controversy. Whether there is an oxygen supply dependency in the setting of critical illness has been debated and may depend on individual patient factors and the methods used to quantify the oxygen use. Past studies performed primarily in surgical patients demonstrated an improved survival in those patients who were managed with strategies to increase tissue oxygen delivery.

Tissue oxygen delivery can be increased using inotropic agents to increase the cardiac output or by increasing the hemoglobin concentration with red blood cell (RBC) transfusions to increase the oxygen carrying capacity of

by mansdocs.com

Table 4: Common clinical and laboratory methods to evaluate specific organ system dysfunction.

Respiratory dysfunction	• Presence of altered oxygenation status, which may be reflected by a decreased PaO_2/FiO_2 ratio and/or requirement of supplemental oxygen • Requirement and duration of mechanical ventilatory support, level of PEEP required and the use of non-conventional ventilator support strategies may help in defining the severity of respiratory dysfunction
Renal dysfunction	• Urine output (oliguria) • Elevated serum creatinine levels • Requirement of renal replacement therapy
Hepatic dysfunction	• Presence of clinical jaundice or hyperbilirubinemia • Elevated serum transaminases, lactate dehydrogenase and/or alkaline phosphatase • Hypoalbuminemia and an elevated prothrombin time may also indicate hepatic dysfunction
Cardiovascular dysfunction	• Manifested as hypotension usually requiring vasopressor and/or inotropic support • Presence of tachycardia, arrhythmias, fatal cardiac rhythms (cardiac arrest) • Increased left heart pressures (pulmonary capillary occlusion pressure, CVP) • *A new concept of the pressure adjusted HR has recently been introduced and is represented by the ratio of the HR and mean arterial pressure*
Hematologic dysfunction	• Thrombocytopenia, leukocytosis or leukopenia • Coagulopathy as evidenced by prolonged prothrombin time, partial thromboplastin time, fibrin degradation products or other evidence of DIC • Excessive bleeding and ecchymoses are also considered in some scoring systems as evidence of organ dysfunction
Gastrointestinal dysfunction	• Intolerance of enteral nutrition support • Gastrointestinal bleeding • Intestinal ischemia or infarction • Viscus perforation • Acalculous cholecystitis
Neurologic dysfunction	• Altered level of consciousness including confusion, delirium and psychosis • Decreased Glasgow Coma scale
Endocrine dysfunction	• Hyperglycemia due to insulin resistance • Hypertriglyceridemia, hypoalbuminemia • Hypercatabolism and accelerated weight loss • Hypoadrenalism
Immune system dysfunction	• Leukocytosis, lymphopenia • Development of healthcare associated secondary infections

(CVP: Central venous pressure; DIC: Disseminated intravascular coagulation; FiO_2: Fraction of inspired oxygen; HR: Heart rate; PaO_2: Partial pressure of oxygen in arterial blood; PEEP: Positive end-expiratory pressure).

the blood. These measures have pros and cons. The use of inotropic and vasoactive agents may be associated with the development of arrhythmias and even ischemia of some selected organ beds. The use of packed RBC transfusions to increase the oxygen carrying capacity of blood needs to be countered by the potential risks, such as immune suppression, microcirculatory dysfunction and transmission of infections. In blood that has been stored for longer than 15 days using citrate phosphate dextrose adenine 1 (CPDA-1) there may be a loss of normal RBC deformability with a potential for microcirculatory dysfunction.

Recent studies suggest that this previously demonstrated oxygen supply dependence may actually reflect mathematical coupling, because this relationship was predominantly evident when the oxygen delivery and the oxygen consumption were calculated using standard formulae.

Potential toxicity has been demonstrated in some patients who were subjected to strategies designed to greatly increase oxygen delivery by inotropic support of the cardiac output.

A large, prospective, randomized, controlled trial failed to demonstrate improved survival using a therapeutic strategy designed to increase the tissue oxygen delivery to supranormal levels. It is important to restore and maintain hemodynamic stability. The initial agent should be fluid to ensure that the circulating intravascular volume is appropriate. There is controversy as to which type of fluid

by mansdocs.com

is preferable, and a discussion of the pros and cons of crystalloid, colloid, blood products and volume expanders are beyond the scope of this chapter. If the use of appropriate type and volume of fluid does not adequately resuscitate the patient, vasoactive medications should be used to improve hemodynamic function and ensure adequate oxygen delivery to the tissues.

Some clinicians advocate the use of gastrointestinal tonometry to assess the adequacy of mesenteric blood flow and intestinal perfusion. A persistently low gastrointestinal pHi and serum lactate concentration have been shown to be associated with increased mortality and the development of MODS/MOF.

The importance of early nutritional support, predominantly using the enteral route, as a means to maintain the integrity of the intestinal mucosal barrier function and decrease the likelihood of bacterial or toxin translocation has recently been emphasized. Enteral nutrition also supports the integrity of the upper gastrointestinal tract and may obviate the need for other agents that are used to prevent stress-related gastrointestinal bleeding. Other potential approaches to prevent stress-related gastrointestinal bleeding include the use of histamine type 2 receptor blockers and cytoprotective agents.

Patients in ICU with MODS are subject to all of the potential complications that may befall the critically ill. Strategies to prevent venous thromboembolism and stress ulcer should be used unless there are specific contraindications.

The development of neuromuscular weakness recently has been recognized as a potential complication in this group of patients and has been termed critical illness polyneuropathy or polymyopathy. The pathophysiology of critical illness polyneuropathy involves primary axonal degeneration that likely results from proinflammatory mediators. It may take up to 3–6 months for the axons to sufficiently recover. These disorders may explain prolonged ventilator dependency in some critically ill patients and may necessitate rehabilitation efforts even after weaning or separation from ventilatory support before the patients are able to return home and care for themselves.

PREVENTION OF MULTIPLE ORGAN DYSFUNCTION SYNDROME

Given that there is no specific therapeutic treatment, attention has turned toward the development of strategies to prevent the development of MODS/MOF. Clinical investigations have undertaken innovative trials aimed at blocking, neutralizing, or removing the potential inflammatory mediators and at designing support strategies using increased tissue oxygen delivery. Unfortunately up to this point, none of these approaches have been demonstrated to be effective in preventing or treating MODS/MOF in the critically ill patient.

Early trials of antiendotoxin therapy with the human and murine monoclonal antibodies against endotoxin demonstrated a decrease in the development of MODS. The murine monoclonal antibody, E-5, also demonstrated increased resolution of established organ dysfunction in the initial trials. However, a subsequent confirmatory trial failed to find a statistical benefit to this form of treatment.

Continuous venovenous hemofiltration is being used in some centers as a means of removing circulating inflammatory mediators. Concern has, however, emerged about the potential for this technique to remove the inflammatory as well as the anti-inflammatory mediators. Studies are ongoing in an attempt to define the role, if any, of antimediator therapy in the management of patients with MODS/MOF.

Prevention has been investigated using the expensive technique of selective digestive decontamination, which couples topical and systemic antimicrobial therapy in an attempt to decrease the development of nosocomial infections and the complications associated with their development. The true benefit of this technique remains to be established. Data have demonstrated prevention of acute respiratory distress syndrome using the thromboxane synthetase inhibitor, ketoconazole, in surgical patients who have increased risk for the development of MODS/MOF.

The activation of the coagulation system and the potential of microthrombi to obstruct the blood flow to vital tissues is currently under evaluation using antithrombin III, activated protein C and tissue factor pathway inhibitor infusions. Antithrombin III has been shown to improve the oxygenation index [partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) ratio] in critically ill patients who were found to have less than 70% antithrombin III activity at baseline. Eisele et al. analyzed several studies of critically ill patients with sepsis or after trauma and reported that there was less organ dysfunction in the patients who had received antithrombin III infusions compared with those treated with placebo. The beneficial value of this therapeutic approach awaits the completion of prospective, randomized, placebo-controlled trials, which are currently underway.

by mansdocs.com

PROGNOSIS

The development of MODS/MOF in a critically ill patient has been associated with a high risk for morbidity and mortality. The onset of organ dysfunction has been heralded as a poor prognostic factor and has been referred to as the major cause of death in the most noncoronary ICUs. The mortality of the patient increases with the number of organ systems failing and the duration of the failure. Studies also have demonstrated that there is a higher risk of mortality associated with some specific organ systems, such as brain, liver, lung and kidney when they become dysfunctional or fail.

Specific scoring systems have been used to quantify the level of organ dysfunction and have been primarily used in the evaluation of various investigational agents. The use of a MODS score has been proposed as a prognostic index. As demonstrated in Table 3, there is an increase in mortality as the MODS score increases. Until we have the ability to provide specific therapy for the treatment of organ dysfunction, rather than just support, we must focus our attention primarily on prevention. It is hoped that in the near future we will have specific forms of therapy in our clinical armamentarium to allow for improved outcomes in these critically ill patients.

Depending on the organs involved, MODS carries a mortality that varies from 30% to 100%. It is clear, however that the greater the number of organs that fail and the longer their duration, the higher the mortality. The mortality (shown in parentheses here) rate increases as the number of organ systems fail as follows:

- Single organ failure (7%)
- Two organs (26%)
- Three organs (50%)
- Four organs (70%)
- Five organs (80%).

It is important to note that the broad range of predicted mortalities for this syndrome will vary depending on the inciting insult and the number of systems involved, and it is disappointing to note that the mortality related to MODS has not changed over the past two decades. This is related to the multifactorial etiology of MODS. Therefore, a single therapeutic agent that improves the outcome of MODS is unlikely.

CONCLUSION

Multiple organ dysfunction syndrome is a complication of interventional technology and the prolonged support of critically ill patients. The syndrome arises from the complex interactions of endogenous and exogenous factors. Treating the cause and supportive therapy remains the mainstay of management of patients with MODS. Since the SIRS is frequently the precursor of MODS, future therapies will be directed to the cellular and molecular bases of this syndrome.

BIBLIOGRAPHY

1. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51.
2. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin. 2000;16(2):337-52, vii.
3. Irwin RS, Rippe JM. Irvin and Rippe's Intensive Care Medicine, 7th edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2011.
4. Jacobs LM. Economic effects of managed care. Surg Clin North Am. 1999;79(6):1249-57.
5. Vincent JL, Abraham E, Moore FA, et al. Textbook of Critical Care, 6th edition Philadelphia, PA: Saunders; 2011.

by mansdocs.com

CHAPTER

7

Cardiopulmonary Resuscitation: A Paradigm Shift

Khusrav Bajan

Sudden cardiac deaths (SCDs) occur mainly at home or outside a hospital setting, and majority of these can be prevented with timely bystander cardiopulmonary resuscitation (CPR) and automated external defibrillator (AED) use. Unfortunately, only 33% of victims of SCDs actually get CPR due to lack of awareness and techniques, inhibitions to do mouth-to-mouth resuscitation, medicolegal implications and more.

Sudden cardiac deaths could arise due to a heart attack, stroke, sedation, overdose, severe hypoglycemia, choking, etc., and it makes it imperative for the bystander or caregiver to be able to differentiate between someone who is unconscious and/or critically ill from someone in cardiac arrest.

The objectives of this chapter would be to identify cardiac arrest without delay and to be able to perform basic life support (BLS) measures to save a life. One should be well versed with the hands-only CPR technique, and also be updated with the newer recommendations and guidelines.

CARDIAC ARREST

Cardiac arrest is defined as cessation of cardiac mechanical activity, which leads to cessation of blood supply to brain and other vital organs. It is characterized as unresponsiveness, absent pulse, absent breathing or agonal breathing (gasping). Cardiac arrest causes death, if not treated in minutes. Therefore, immediate recognition and prompt resuscitation is mandatory for a favorable outcome.

In this chapter, basics of CPR along with history, epidemiology and current trends will be discussed.

CARDIOPULMONARY RESUSCITATION

Cardiopulmonary resuscitation includes series of life saving actions that improve the chance of survival after cardiac arrest. The CPR mainly consists of chest compressions, artificial breathing, defibrillation and drugs.

Worldwide, American Heart Association (AHA) and International Liaison Committee on Resuscitation (ILCOR) guidelines are followed, which are reviewed every 5 years.

HISTORY OF CPR

The practice of CPR has evolved over many centuries, with the first accounts dating back to biblical times. However, consistently recorded medical success of CPR methods only appeared in the early nineteenth century.

Ancient Hebrew scripture and the Old Testament both describe the resuscitation of a young boy by the prophet Elijah. This is possibly the first documented account of life support.

There were life support measures like barrel method, trotting horse method or immersion in hot oil baths, prevalent before eighteenth century, but more effective methods of BLS were proposed in mid-eighteenth century.

Vesalius was the first to introduce artificial respiration and airway control in 1555, when he used a reed placed in trachea of animals to keep them alive while studying their anatomy. Tossach performed first documented mouth-to-mouth resuscitation on a coal miner. In 1958, Safar,

by mansdocs.com

Escarraga and Elam published first definitive study on superiority of mouth-to-mouth resuscitation over manual methods.

In 1880, Niehaus performed first unsuccessful attempt at closed cardiac massage in a man.

Early in twentieth century, Crile wrote an extraordinary report on animal resuscitation combining the use of thoracic compression, artificial respiration and epinephrine infusion.

In 1960, Kouwenhoven, Jude and Knickerbocker reported successful use of closed cardiac compressions in 20 patients ranging in age between 20 months and 80 years.

In 1947, Claude performed first successful internal defibrillation in operating room, and in 1956, Zoll performed first human external defibrillation.

The success of Crile, Kouwenhoven and many other scientists formed the basis of BLS and opened the door for advanced cardiac life support (ACLS).

EPIDEMIOLOGY

Each year, approximately 383,000 persons in United States suffer out-of-hospital cardiac arrest (OHCA), and about 75–80% of cardiac arrest cases occur at home. Coronary heart disease accounts for about 550,000 of the 927,000 adults who die as a result of cardiovascular disease.

The AHA published 2013 update on statistics, highlights of this document are given in Table 1.

Unfortunately, we do not have authentic Indian CPR statistics reporting annual incidence and survival rates. In 2011, a study by Madhavan SR, et al., reported that cardiovascular disease was the underlying cause in majority of sudden cardiac arrest events during a study period of 22 months involving total deaths of 1,916.

BASIC LIFE SUPPORT

In this chapter, 2010 AHA guidelines will be discussed, which is followed worldwide. The 2010 AHA guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (CPR and ECC) are based on an international evidence evaluation process that involved hundreds of international resuscitation experts who evaluated, discussed, and debated thousands of peer-reviewed publications.

Table 1: Incidence of cardiac arrest in USA.

	Out-of-Hospital Cardiac Arrest			*In-Hospital Cardiac Arrest*	
Statistical Update	*Incidence*	*Bystander CPR*	*Survival Rate*	*Incidence*	*Survival Rate*
2013	359,400	40.1%	9.5%	209,000	23.9%
2012	382,800	41.0%	11.4%	209,000	23.1%

Key Changes and Highlights of 2010 AHA Guidelines

1. The simplified universal adult BLS algorithm (Fig. 1) has been created, so as to simplify lay rescuer training and to continue to emphasize the need to provide early chest compressions for the victim of a sudden cardiac arrest.
2. Refinements have been made to recommendations for immediate recognition and activation of the emergency activation system once the health care provider identifies the cardiac arrest victim, who is unresponsive with no breathing or agonal breathing (gasping).

Rationale: simple and easy way for quick identification of cardiac arrest victim, so that initiation of CPR can be achieved without any delay.

3. Look, listen and feel for breathing has been removed.

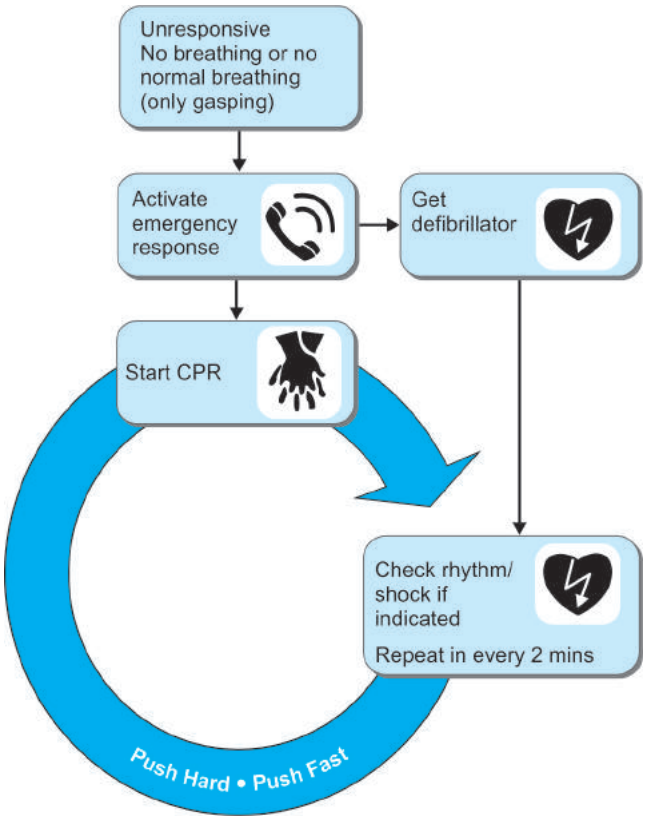


Fig. 1: Simplified adult BLS algorithm.

by mansdocs.com

Rationale: Breathing is briefly checked as part of a check for recognition of cardiac arrest, so that early compressions can be delivered.

4. Increased emphasis on high quality CPR, as chest compressions are the mainstay of CPR :
   - Compressions of adequate rate, atleast 100/min.
   - Compressions of adequate depth, atleast 2 inches in adult.
   - Allowing complete chest recoil.
   - Minimizing interruptions.
   - Avoiding excessive ventilation.
5. C-A-B (Compression-Airway-Breathing) rather than A-B-C (Aiway-Breathing-Compression) rather than ABC, that means rescuers should initiate chest compressions first before giving rescue breaths.

   Rationale: There is enough oxygen levels in blood in initial few minutes of cardiac arrest and chest compressions provide vital blood flow to the heart and brain and hence ensuring oxygen supply. Chest compressions can be started immediately, whereas positioning the head and achieving the seal for mouth-to-mouth or bag-mask rescue breathing all take time.
6. Compression rate is modified to atleast 100/min from approximately 100/ min.

   Rationale: In most studies, delivery of more compressions during CPR is associated with better survival.
7. Compression depth for adults has been slightly altered to atleast 2 inches (about 5 cm) from previous recommended range of about 1.5–2 inches.

   Rationale: Compressions generate critical blood flow and oxygen delivery to heart and brain. Confusion may result when there is a range of recommendation for depth, so one compression depth is recommended.
8. Continued emphasis on the need to reduce the time between the last compression and shock delivery and the time between shock delivery and resumption of compressions.
9. Use of cricoid pressure is generally not recommended.
10. There is increased focus on using a team approach during CPR.
11. Automated external defibrillators are integrated in to chain of survival system for public places. The use of AEDs can be considered for hospital use as well. AED use in children now includes infants.

CHAIN OF SURVIVAL

In the first few minutes following OHCA swift implementation of five critical actions by bystanders and emergency medical services providers can substantially increase chances of survival with good neurological outcome (Fig. 2).

Hands-Only CPR or Cardio Cerebral Resuscitation (CCR)

It is a potentially lifesaving technique involving no mouth to mouth contact but only chest compressions. It is best used in witnessed cardiac arrest and if bystander is not trained in CPR.

Hands-only CPR substantially improves survival rates following adult OHCA compared with no bystander CPR.

Observational studies of adults with cardiac arrest showed similar survival among victims receiving hands-only CPR versus conventional CPR with rescue breaths.

Advantages

- Reluctance to perform mouth-to-mouth ventilation is potential barrier to performing bystander CPR which can be overcome by hands-only CPR.
- Hands-only CPR is easier for an untrained rescuer to perform and can be readily guided by dispatchers on phone.

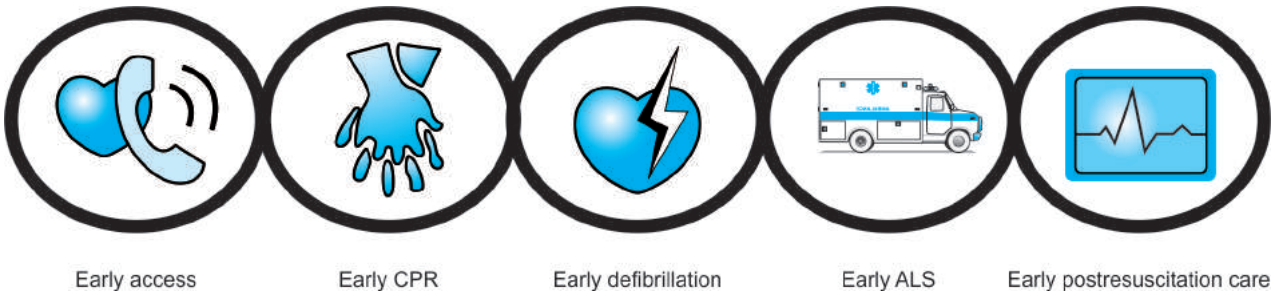


Fig. 2: Chain of survival.

by mansdocs.com

- Growing evidence of chest compressions and the reality that setting up airway equipment takes time.
- Oxygen levels in blood remain adequate for first several minutes after cardiac arrest and it is crucial to maintain blood flow with chest compressions.
- Many cardiac arrest victims exhibit gasping or agonal breathing and gas exchange allows for some oxygenation and CO_2 elimination.
- Passive chest recoil during relaxation phase of chest compressions can also provide some air exchange.

Limitations

- Hands-only CPR not recommended in pediatric population.
- Not reliable in unwitnessed cardiac arrest.
- The precise interval for which performance of hands-only CPR is acceptable is not known at this time, as at some time during prolonged CPR supplementary oxygen with assisted ventilation is necessary.

ADVANCED CARDIAC LIFE SUPPORT

Key Issues and Major Changes

1. Quantitative waveform capnography is recommended for confirmation and monitoring of endotracheal tube placement and quality of CPR (Fig. 3).

Rationale: It is the most reliable method of confirming and monitoring correct placement of endotracheal tube. Because blood must circulate through the lungs for CO_2 to be exhaled and measured, capnography can also serve as a physiologic monitor of the effectiveness of chest compressions. During CPR, an end-tidal CO_2 ($ETCO_2$) of more than 10 mm Hg should be targeted. Falling cardiac output or rearrest in the patient with return of spontaneous circulation (ROSC) also causes a decrease in $ETCO_2$, whereas ROSC may cause an abrupt increase in $ETCO_2$.

2. The traditional cardiac arrest algorithm simplified in the form of circular algorithm to emphasize on high quality CPR (Fig. 4).
3. Atropine is no longer recommended for routine use in the management of Pulseless electrical activity (PEA)/Asystole.
4. Chronotropic drug infusions are recommended as an alternative to pacing in symptomatic and unstable tachycardia.
5. Adenosine is recommended as safe and potentially effective for both treatment and diagnosis in the initial management of undifferentiated regular monomorphic wide-complex tachycardia.
6. Systemic post-cardiac arrest care after ROSC should continue in critical care unit, which should include cardiopulmonary and neurologic support. Therapeutic hypothermia should be provided to those who are unconscious after ROSC. Percutaneous coronary interventions should be offered in case of STEMI.
7. *Shock therapy*: Indicated for shockable rhythms; ventricular fibrillation (VF) (Fig. 5) and pulseless ventricular tachycardia (VT) (Fig. 6). Shock energy for biphasic should be as per manufacturer's recommendation (120-200J), if unknown, then use maximum available and in case of monophasic defibrillators, use 360J.
8. Advanced cardiac life support also includes drug therapy (intravenous or intraosseous). Adrenaline 1 mg every 3–5 minutes is to be used in both shockable and non–shockable rhythm. Vasopressin 40 IU can replace either first or second dose of adrenaline. Amiodarone is to be used in cases of refractory VF/VT.
9. Differential diagnoses (5 Hs and 5 Ts) (Table 2) should always be sought so as to determine the cause of cardiac arrest.

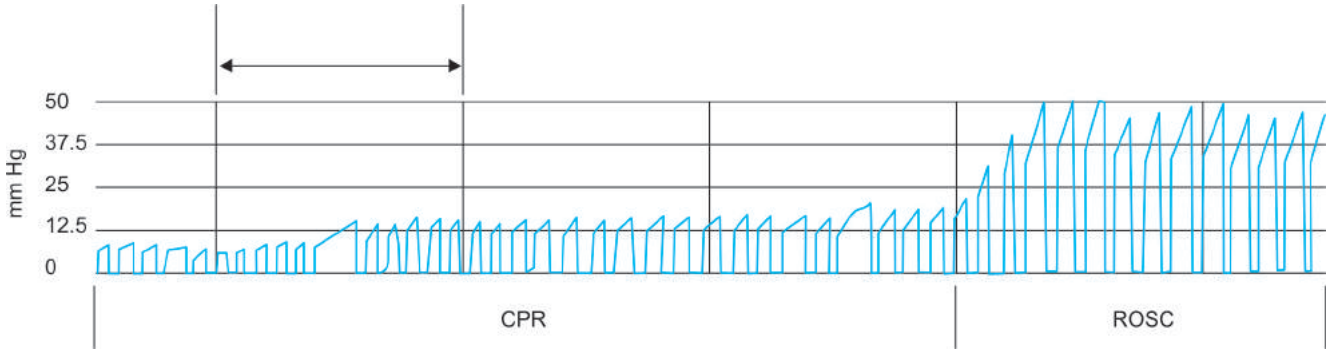
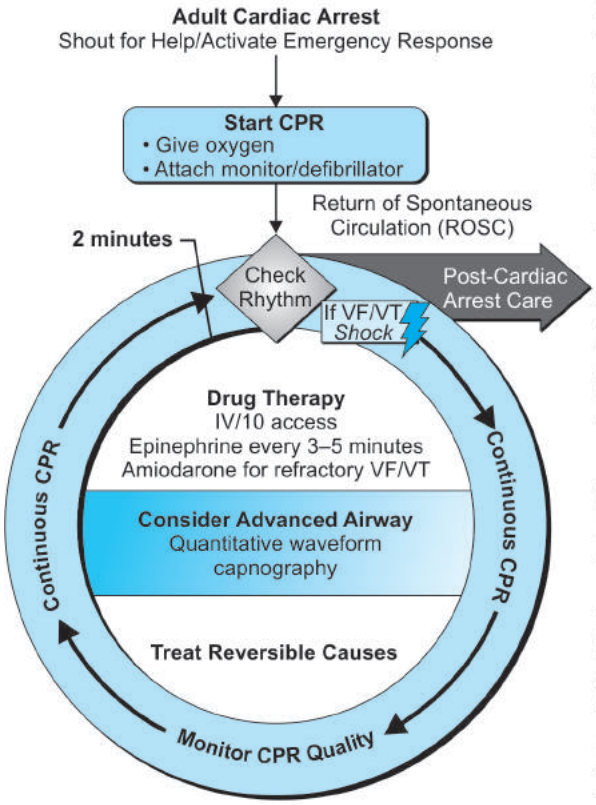


Fig. 3: Capnography to monitor effectiveness of resuscitative efforts.

by mansdocs.com



CPR Quality
- Push hard (≥2 inches [5 cm] and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If $PETCO_2$ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in $PETCO_2$ (typically ³40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock Energy
- **Biphasic:** Manufacturer recommendation (e.g. initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy
- **Epinephrine IV/IO Dose:** 1 mg every 3–5 minutes
- **Vasopressin IV/IO Dose:** 40 units can replace first or second dose of epinephrine
- **Amiodarone IY/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 8-10 breaths per minute with continuous chest compressions

Reversible Causes
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

Fig. 4: Circular ACLS algorithm.

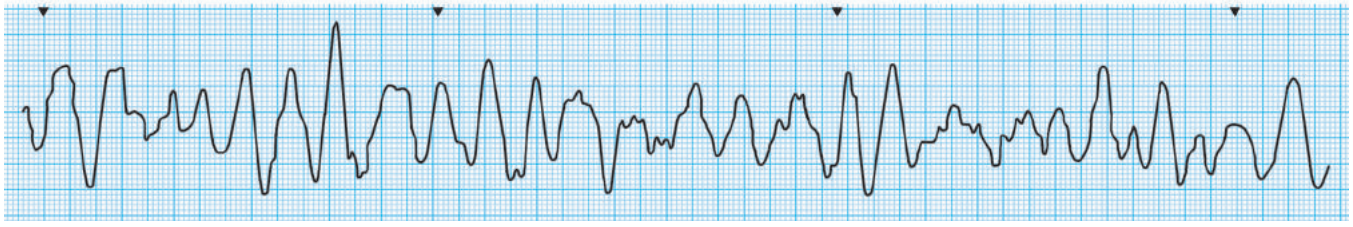


Fig. 5: Ventricular fibrillation.

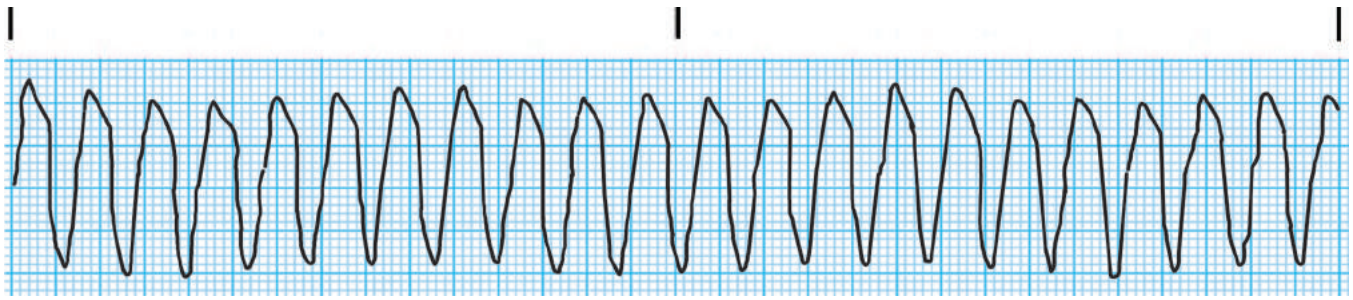


Fig. 6: Ventricular tachycardia.

by mansdocs.com

Table 2: Differential diagnosis with 5Hs and 5 Ts.

5 Hs	*5 Ts*
Hypoxia	Toxins
Hypovolemia	Tension pneumothorax
Hydrogen ions acidosis	Temonade cardiac
Hypo-/hyperkalemia	Thrombosis cardiac
Hypothermia	Thrombosis pulmonary

CONCLUSION

Death from sudden cardiac arrest is not inevitable. Identification of cardiac ACLS arrest victim and initiation of high quality CPR without any delay improves survival rates with favorable neurological outcome. In case of OHCA, effective bystander CPR, can double victim's chance of survival. ACLS is effective only when it is preceded by timely initiated and performed BLS. Integrated post-cardiac arrest care should continue after ROSC. Success of CPR depends on team effort.

BIBLIOGRAPHY

1. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and Emergency Cardiovascular Care. www.heart.org.
2. Benjamin M. Scirica,Therapeutic hypothermia after cardiac arrest, clinical update, Circulation. 2013;127:244-50.
3. CPR facts and statistics, American Heart Association, 2013 update. www.heart.org.
4. Field JM, Hazinski MF, Sayre M, et al. Part 1: Executive Summary of 2010 AHA Guidelines for CPR and ECC. Circulation. Circulation 2010;122:S640-56.
5. History of cardiopulmonary resuscitation, Cardiology journal. 2009;16:487-88.
6. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. JAMA. 1960.
7. Nolan JP, Hazinski MF, Billi JE, et al. Part 1: Executive Summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation. 2010;81 Suppl 1:e1-25.
8. SN Narasingan, Contemporary management of sudden cardiac death. www.apiindia.org/medicine_update_2013/Chapter 31.

by mansdocs.com

CHAPTER

8

Therapeutic Hypothermia

Pinak Ashok Shrikhande

INTRODUCTION

After return of spontaneous circulation (ROSC), postcardiac arrest care starts with transportation of patient to appropriate critical care unit in case of in hospital cardiac arrest and to appropriate hospital in case of out-of-hospital cardiac arrest (OHCA). Cardiac arrest highlights one of the critical interactions between the heart and the brain. The goal of resuscitation for a patient in cardiac arrest is to support and restore effective oxygenation, ventilation and circulation with return of intact neurological function. The most important determinants of survival after cardiac arrest are cardiovascular instability and brain injury. The main objective of postcardiac arrest care is to determine and treat the cause of arrest and ensure adequate perfusion to the organs especially brain.

The functional and metabolic effects of ischemia on brain depend upon the severity and duration of reduction in cerebral blood flow (CBF). The brain needs a constant supply of glucose and oxygen—receives 25% of total glucose consumption, 20% of total oxygen consumption and 15–20% of total cardiac output in resting state. Normal CBF in humans is 50 mL/min/100 g of brain tissue. Irreversible neuronal damage occurs when CBF drops below 10–15 mL/min/100 g. The lower the CBF, the shorter the time required for irreversible injury. Cerebral metabolic rate of oxygen (cerebral metabolism) ($CMRO_2$), arteriojugular venous difference of oxygen (oxygen extraction) ($AVDO_2$) are highly coupled as $CMRO_2$ = CBF X $AVDO_2$ (Fick's principle). Under normal circumstances, the brain maintains a constant $CMRO_2$ either by changes in cerebral metabolism or CBF—referred to as auto-regulation. Initially as CBF decreases, $AVDO_2$ increases; as the brain compensates for reduced flow by extracting greater amount of oxygen and $CMRO_2$ remains unchanged. As CBF decreases further, e.g. in cardiac arrest, increased extraction of oxygen is not able to compensate and $CMRO_2$ decreases, which leads to inappropriate release of excitatory amino acid neurotransmitters such as glutamate, initiating cell damage by excessive influx of calcium ions through NMDA-type glutamate receptors. This cellular elevation of calcium ions further leads to free radical generation and mitochondrial injury resulting in cell death and cerebral ischemia/infarction occurs. If ROSC is achieved, secondary cerebral derangements occur mainly due to free radical production, which further lead to death of vulnerable neurons.

Therapeutic hypothermia (TH) has shown to produce salutary chemical and histological effects in animal models of acute neuronal injuries. But, unfortunately those findings have not been translated into better outcomes in human studies. The only exception is treatment of patients with diffuse ischemic brain injury after cardiac arrest. Two randomized controlled trials (RCTs) published simultaneously in 2002 evaluated out-of-hospital postcardiac arrest survivors who were unconscious and had initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT). The largest study conducted by "The Hypothermia After Cardiac Arrest (HACA) study group"; a multicenter randomized control trial included 136 patients, who had been resuscitated after OHCA due to VF. Patients who had—severe hypothermia (temperature

by mansdocs.com

< 30°C) on admission, hypotension [mean arterial pressure (MAP) < 60 mm Hg] for more than 30 minutes after ROSC, hypoxemia (SpO_2 < 85%) for 15 minutes after ROSC—were excluded from the study. Patients were induced hypothermia with target temperature of 32–34°C within 4 hours after ROSC. The target temperature was maintained for 24 hours and rewarming was done passively, which expected to rewarm the patients in 8 hours. The patients in hypothermia group were found to have favorable neurological outcome as compared to normothermia group (55% versus 39% respectively). The 6 month mortality was also low in hypothermia group (41% versus 55%). Bernard et al. conducted a RCT with 77 patients who remained unconscious after resuscitation from OHCA. Patients were cooled to core temperature of 33°C within 2 hours of ROSC and maintained at that temperature for 12 hours and beginning from 18th hour, patients were actively rewarmed for next 6 hours. They observed that 49% of patients in hypothermia group had survived and with good neurological outcome as compared to 26% in normothermia group. Both of these RCTs showed significantly improved neurological outcome and better survival with mild TH in OHCA patients with initial rhythm of VF/VT. A subsequent meta-analysis concluded that number needed to treat (NNT) the cardiac arrest patients with initial rhythm of VF/VT is six. American Heart Association (AHA) guidelines for cardiopulmonary resuscitation and emergency cardiovascular care has recommended that comatosed adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32–34°C. The outcome may be different for in hospital versus OHCA or VF/VT versus asystole pulseless electrical activity (PEA) cardiac arrest.

The role of hypothermia in traumatic brain injury (TBI) patients is less clear. The studies have been done for induced hypothermia either in unselected TBI patients with hypothermia as a neuroprotective modality or in TBI patients with high intracranial pressure (ICP) as a measure to reduce ICP. The "National Acute Brain Injury Study: Hypothermia" confirmed that induced hypothermia is not effective in improving long-term outcomes in unselected severe TBI patients. Further data analysis suggested that patients who were hypothermic on admission had a lower percentage of poor outcome when they were assigned to hypothermia rather than normothermia. But the recently conducted "National Acute Brain Injury Study: Hypothermia II" trial studied severe TBI patients with "early induction" of hypothermia; could not demonstrate the utility of hypothermia as a neuroprotective strategy. It remains possible that hypothermia may be beneficial when instituted only for those head injury patients with demonstrated high ICP.

The exact mechanism by which TH results in reduced cerebral damage is unclear. In normal brain, $CMRO_2$ decreases by 6–7% for every 1°C decrease in temperature. The beneficial effect of TH in patients who remain comatose after ROSC, may be due to decrease in free radical production, release of excitatory amino acids or calcium shifts, protection of lipoprotein membrane or may be reduction of oxygen demand in low flow areas of brain.

Patient Selection

Therapeutic hypothermia is applied to those adult cardiac arrest patients who have ROSC and are unresponsive after that. The patients should be hemodynamically stable and able to maintain oxygenation with mechanical ventilation. TH should not be instituted in patients who have other causes of coma present, bleeding diathesis or taking anticoagulants or ongoing bleed, presently have sepsis or increased risk of infection, do not resuscitate (DNR) or do not intubate (DNI) status.

Therapeutic hypothermia occurs in three phases—induction, maintenance and rewarming.

INDUCTION PHASE

Hypothermia is classified as:

- *Mild*: Temperature 32–35°C
- *Moderate*: Temperature 28–32°C
- *Severe*: Temperature below 28°C.

Therapeutic hypothermia requires cooling of whole body rather than regional cooling of brain with cooling helmets. TH should be initiated as soon as possible after ROSC. It may be successful even if delayed by 4–6 hours. The temperature should be brought down to 32–34°C (mild hypothermia). Following methods can be used to achieve TH.

External Cooling

The physiological mechanisms by which body loses heat are: conduction, convection, radiation and evaporation.

- Skin-surface cooling with a circulating-water mattress and blanket. The water temperature is set to 5°C. The mattress and blanket are positioned directly on the skin and the entire body below the neck is covered. They are the best studied and rapid means of controlling body temperature. Water blankets require no invasive procedures.

by mansdocs.com

- *Cold air-forced cooling*: Surface cooling with a full-length cover attached to a forced-air cooler. This device provides 1,000 L/min air at 10°C. It is effective, risk free and can be implemented rapidly.
- Ice packs can be applied on armpits, head/neck and groin. This method decreases the temperature very slowly and is highly variable.
- Wet towels/sheets and fanning.
- *Immersion in an ice and water slurry*: Decreases core temperature rapidly, but difficult to implement.

Internal Cooling

- *Intravenous (IV) heat exchange devices:* This technique uses the endovascular heat exchange catheters. Cold saline enters the catheter and passes through the coils with large surface areas and heat exchange takes place between these coils and blood. This ensures rapid cooling and controls temperature precisely. Temperature can be maintained tightly and rewarming can be controlled actively. But there is a risk of infection and of bleeding at the insertion site. A major limitation is the high cost of the devices (Figs. 1 and 2).
- *Cold IV fluids:* Ice cold IV fluids (4°C) have been used in various physiological studies. Each liter of fluid given at 4°C decreases mean body temperature by 0.5°C. Induction of hypothermia by means of cold IV infusion is fast, efficacious and safe. The method is restricted by the volume that can be administered without overloading the cardiovascular system. It should be followed by another method to maintain hypothermia, such as cooling blankets.
- *Gastric lavage*: Using sterile water instilled via an orogastric tube. The cold fluid (nearly = 500 mL) is allowed to flow into the stomach under gravity and then aspirated 5 minutes later. Each cycle lasts about 10 minutes. It provides moderate core cooling but may lead to abdominal cramping and diarrhea.
- Bladder lavage using Ringer's solution is instilled via a double-lumen urethral catheter. The cold fluid (nearly 300 mL) is allowed to flow into the bladder under gravity and then aspirated 5 minutes later. Each cycle lasts about 10 minutes. It provides only trivial heat loss.
- *Peritoneal/pleural lavage*: Core cooling rates have not been evaluated specifically during peritoneal lavage. A disadvantage of peritoneal lavage is that the procedure is invasive and requires a level of skill.
- *Extracorporeal cooling*: Partial cardiopulmonary bypass is extremely invasive and requires considerable skill with special equipment. Even in hospitals where the technique is available, cardiopulmonary bypass will certainly require far longer to initiate than other invasive core cooling methods.

MAINTENANCE PHASE

Hypothermia should be maintained for 12–24 hours from the time the target temperature was achieved. It is important to monitor patient's comfort and need for sedation and/or muscle relaxant. If muscle relaxant is used, neuromuscular monitoring should be done. Shivering should be avoided as it may increase oxygen demand of the brain. Regular charting of neurological status of patient should be done.

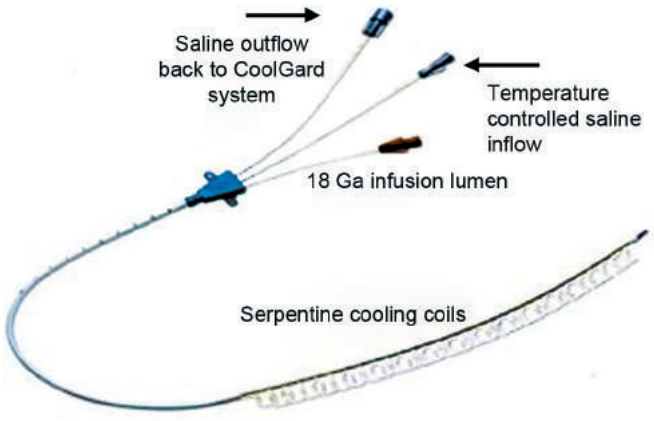


Fig. 1: Intravascular heat exchange catheter.



Fig. 2: Intravascular heat exchange device.

by mansdocs.com

Monitoring of temperature: Core body temperature should be monitored while inducing TH. Pulmonary artery catheter temperature is considered as the "Gold Standard" for the measurement of core body temperature. Core temperature can also be measured using nasopharyngeal, rectal or urinary bladder probes; or tympanic temperature monitors. Urinary bladder and esophageal electronic thermometers are more reliable than the electronic rectal thermometer. Rectal temperature significantly lags behind other core sites such as the esophageal site, especially during acute temperature alterations. Tympanic thermometry is not reliable in critically ill patients. Axillary and inguinal temperature measurements do not correlate well with core temperature and do not allow continuous monitoring in intensive care units.

REWARMING PHASE

It is very important to control temperature during rewarming; patient should be rewarmed slowly at the rate of 0.15°C–0.50°C to target temperature of 36°C over a period of 12 hours as there is a potential risk of rebound hyperthermia. Controlled rewarming should be done; internal device may be used to control the rewarming temperature during rewarming. Patient may be rewarmed passively—active rewarming using warm air blankets should not be done.

Patients may need volume resuscitation during rewarming phase because of vasodilation caused by rise in body temperature. Because electrolytes shift out of the cells back into the serum during rewarming, frequent electrolyte monitoring is needed during this phase to prevent critically elevated levels. Slow, controlled rewarming allows the kidneys to excrete excess potassium, preventing hyperkalemia. Glucose levels should be monitored frequently as insulin resistance of hypothermic phase now diminishes and may lead to hypoglycemia.

Adverse Effects of Therapeutic Hypothermia

Cardiovascular: Increased systemic vascular resistance (SVR), bradycardia, atrioventricular blocks, atrial and ventricular arrhythmias (occur mainly if temperature is less than 30°C).

Infection: Hypothermia reduces the number and function of WBCs, but this happens mostly during prolonged hypothermia. This may increase the risk of developing pneumonia. However, it is relatively uncommon in brief periods of TH (12–24 hours).

Renal: Induction of TH causes mild diuresis, because of increased venous return due to vasoconstriction and due to decreased antidiuretic hormone levels. Hypothermia shifts potassium into the cells leading to hypokalemia. Replacement of potassium during hypothermia phase poses a risk of hyperkalemia during rewarming.

Gastrointestinal: Hypothermia decreases gut motility, which may lead to delayed enteral feeding.

Metabolic: Hypothermia causes hyperglycemia, because of insulin resistance. This may require glucose control by insulin administration.

Coagulopathy: Hypothermia leads to deranged coagulation profile and decreased platelet count.

In spite of recommendations given by AHA, the use of TH in post-cardiac arrest patients is still very low. A prospective cohort study conducted on about 67,500 patients, who had ROSC after in-hospital cardiac arrest, concluded that TH was used rarely (only in 2% of patients) and once instituted target temperature was commonly not achieved (44.3% patients did not achieve target temperature and 17.6% patients were overcooled).

BIBLIOGRAPHY

1. Al-Senani FM. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. Resuscitation. 2004;62(2):143-50.
2. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia–the ischemic penumbra. Stroke. 1981;12(6): 723-35.
3. Bernard S, Buist M, Monteiro O, et al. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: A preliminary report. Resuscitation. 2003;56:9-13.
4. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557-63.
5. Clifton GL, Miller ER, Choi SC, et al. Hypothermia on admission in patients with severe brain injury. J Neurotrauma. 2002;19:293–301.
6. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med. 2001;344:556-63.
7. Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. Lancet Neurol. 2011;10:131–39.
8. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med. 2005;33:414-8.

by mansdocs.com

9. Lefrant JY, Muller L, Emmanuel Coussaye J, et al. Temperature measurement in intensive care patients: comparison of urinary bladder, oesophageal, rectal, axillary, and inguinal methods versus pulmonary artery core method. Intensive Care Med. 2003;29:414–8.
10. Michael Holzer. Efficacy and Safety of Endovascular Cooling After Cardiac Arrest. Stroke. 2006;37:1792-7.
11. Mikkelsen ME, Christic JD, Abella BS, et al. Use of therapeutic hypothermia after in-hospital cardiac arrest. Crit Care Med. 2013;41:1385–95.
12. Molnar GW, Read RC: Studies during open-heart surgery on special characteristics of rectal temperature. J Appl Physiol. 1974;36:333–6.
13. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122: S768-86.
14. Plattner O, Kurz A, Sessler DI, et al. Efficacy of intraoperative cooling methods. Anesthesiology. 1997;87:1089–95.
15. Polderman KH, Tjong Tjin Joe R, Peerdeman SM, et al. Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury. Intensive Care Med. 2002;28:1563–73.
16. Robinson J, Charlton J, Seal R, et al. Esophageal, rectal, axillary, tympanic, and pulmonary artery temperatures during cardiac surgery. Can J Anaesth. 1998;45:317–23.
17. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol. 1954;179:85–92.
18. Schmitz T, Bair N, Falk M, et al. A comparison of five methods of temperature measurement in febrile intensive care unit patients. Am J Crit Care. 1995;4:186–92.
19. Staven K, Saxholm H, Smith-Erichsen N. Accuracy of infrared ear thermometry in adult patients. Intensive Care Med. 1997;23:100–5.
20. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. New Engl J Med. 2002;346: 549-56.

by mansdocs.com

CHAPTER

9

Management of Organ Donor

Rajesh Pande

INTRODUCTION

A potential organ donor is defined by the presence of either brainstem death or a catastrophic injury to the brain with the physician's and the family's intent to withdraw life support. "Brainstem death" means the stage at which all functions of the brain stem have permanently and irreversibly ceased and is so certified under subsection (6) of section 3. A "deceased person" means a person in whom permanent disappearance of all evidence of life occurs, by reason of brainstem death or in a cardiopulmonary sense.

WHEN TO TEST FOR BRAIN-DEATH?

It is important that the cause of irreversible structural brain damage should be known and functional reversible causes of a nonfunctioning brainstem have been ruled out. It is important to exclude causes that may result in a similar clinical picture like primary hypothermia, alcohol intoxication, neuromuscular blockades (like use of muscle relaxants), use of central nervous system (CNS) depressant drugs like use of sedatives, severe metabolic or endocrine disturbances. If possible check and rule out for any circulating therapeutic levels of a drug that could cause coma.

TESTS OF BRAINSTEM DEATH

- Fixed pupils not responding to sharp changes in the intensity of incident light.
- No corneal reflex.
- Absent occulo-vestibular reflexes—no eye movements following the slow injection of at least 50 mL of ice-cold water into each ear in turn (the caloric reflex test).

No cough reflex to bronchial stimulation or gagging response to pharyngeal stimulation.

Apnea Test:

- No observed respiratory effort in response to disconnection of the ventilator for long period (typically 5 minutes) to ensure elevation of the arterial partial pressure of carbon dioxide to at least 6.0 kPa/45 mm Hg (6.5 kPa/48 mmHg in patients with chronic carbon dioxide retention).
- Adequate oxygenation is ensured by preoxygenation and diffusion oxygenation during the disconnection (so the brainstem respiratory center is not challenged by the ultimate, anoxic, drive stimulus). It should be noted this is a dangerous—potentially lethal test.

Authorized people who can certify brain death as per THOTA in a hospital: The registered medical practitioner (RMP) in charge of the hospital in which brainstem death has occurred, usually the Medical Superintendent (MS), independent RMP, being a specialist, to be nominated by the RMP specified above (MS), from the panel of names approved by the appropriate authority, a neurologist or a neurosurgeon to be nominated by the RMP specified above (MS), from the panel of names approved by the appropriate authority, the RMP treating the person whose brainstem death has occurred (Primary Physician).

The cadaveric organ donation in India is very low at 0.05/million, compared to 5/million population in Hong

by mansdocs.com

Kong and 25/million population in the US. When we look at the states, there is good awareness in the southern states as compared to the north. 2011 data from Tamil Nadu shows a total of 220 organ donors donated 1,257 organs including 409 kidneys, 341 corneas, 270 heart valves, 197 livers, 35 hearts, 4 lungs and 1 skin. Data from Andhra Pradesh Organ Statistics (Jan–Dec 2011) showed 87% success in organ procurement with a total of 148 organs being procured including 82 corneas, 14 livers, 38 kidneys, 22 heart valves and 2 hearts.

Surveys conducted on awareness regarding the concept of brain death have presented very poor figures—18% among medical postgraduates. (Saudi J Kidney Dis Transpl. 2009; 20:174-180). It has been realized that a large pool of brain-dead patients exist who could become potential organ donors. Their organs are not being utilized for various support logistics. (Transplant Proceed. 2007;39:314-8).

Key elements to the success of the cadaveric organ donation program include:

- Need to educate our own medical fraternity and seek their cooperation.
- The program requires trained counselors to be able to work in the intensive cares.
- The government's support is pivotal if this program is to provide benefit to the common man.

CLASSIFICATION OF ORGAN DONORS

- Donation after brain death
- Heart beating donors
- Nonheart beating donors
- Donation after cardiac death.

Organ donation after cardiac death has been accepted practice for the last 15 years in the west. Decision to withhold life-sustaining therapy precedes donation and is independent of the decision to donate, which mitigates conflict. It is important that the team determining death is strictly separated from the procurement team.

The discussion in this chapter is limited to the donor management after brain death. Irreversible loss of brainstem function due to progression to brainstem death can be induced by multiple pathologies: trauma, secondary swelling, hypoxic brain-injury, and intracranial hemorrhage. The physiological changes can vary, particularly in duration, but careful review of observation charts can reveal the timing of final damage. The features seen in these patients include signs of increased intracranial pressure (ICP), bradycardia, hypertension and sympathetic storm.

DIFFERENT LEVELS OF CARE REQUIRED IN BRAIN-DEAD PATIENTS

- Provide good ICU care and do brainstem death (BSD) testing.
- After brainstem death testing, continue ICU care maintaining the potential for donation.
- If brainstem death presents, refer to transplant co-ordinator for a discussion with relatives.
- Continue with donor management

Changes following brainstem death can affect all the organ systems including cardiovascular, hypothermia, diabetes insipidus, disseminated intravascular coagulopathy (DIC), pulmonary, inflammation.

Incidence of Changes After Brain Death

• Hypotension	81%
• Diabetes Insipidus	65%
• DIC	28%
• Cardiac arrhythmias	25%
• Pulmonary oedema	18%
• Metabolic acidosis	11%

PRINCIPLES OF DONOR MANAGEMENT

All donors are potential multiorgan donors and aim is to make all organs transplantable as well as maintain or improve function. The goals of intensive care is to increase numbers of donors, increase number of organs per donor and improve the function of transplantable organs. Good donor management leads to better outcome. Many studies have shown that high sodium in liver donor doubles the graft loss (Totsuka Transplant Proc. 2000; 32;322–6) and the use of protocols increase the organs per donor from 3.1 to 3.8 as well as increase the probability of transplant (Rosendale Transplantation. 2003;(4):482–7). Data shows that 54% of Australian lung donations were used for transplant versus 13% in UK (Snell J Heart Lung Transplant. 2008;27:662-7).

Basic goals are directed towards maintaining the general stability of the patient with the following target values: mean arterial pressure (MAP) 60–80 mm Hg, central venous pressure (CVP) 6–8 mm Hg, HR 60–100/min, rhythm sinus, cardiac index > 2.1 l/min/m^2. Basic care is the continuum of ICU care, temperature control, methylprednisolone, review of on-going drugs and following the established donor management guidelines.

by mansdocs.com

Bacteremia or fungemia are not absolute contraindications to donation. Organs transplanted from bacteremic donors rarely transmit bacterial infection, and the data suggests that the outcomes for the recipients of organs from donors who have had infection are not significantly worse than those when donors do not have infection. Organs from potential donors infected with hepatitis B or C virus may be transplanted into recipients infected with the same virus and may be considered for those who are not infected and who are in need of a life-saving transplantation.

Absolute contraindications to donation are infection with the human immunodeficiency virus, human T-cell leukemia–lymphoma virus, systemic viral infections (e.g. measles, rabies, adenovirus, enterovirus, and parvovirus), prion-related disease, and herpetic meningoencephalitis.

ORGAN DONOR MANAGEMENT

Hemodynamic targets that should be maintained until organ procurement: Assess using simple monitoring and echocardiographic assessment:

MAP ≥ 60 mm Hg
CVP 6–8 mm Hg
LVEF ≥ 45%
$SCVO_2$ ≥ 60%

Serial lactate should be monitored in all patients and if the levels are high or rising appropriate evaluation should be done to find the etiology.

If the patient is hemodynamically unstable or the above targets are not being, a pulmonary artery catheter may be inserted targeting the following values: pulmonary capillary wedge pressure (PCWP) 8–12 mm Hg, cardiac index ≥ 2.1 L/min, SVR 800–1200 dynes.sec.cm^5, left ventricular stroke work index > 15g.meters/cm^5/beat.

The patients may be treated with fluids or diuretics based on the CVP or PCWP values and/or vasopressor therapy and/or inotropes. Generally, the indications for insertion of a pulmonary artery catheters would be left ventricular ejection fraction (LVEF) < 40% on ECHO assessment, patients requiring high vasopressors or increasing requirement.

Hemodynamic support: Vasopressin should be used as the preferred agent when vasopressors are indicated. The maximum dose can be 2.4U/hr (0.04U/min). The second line agents can be norepinephrine, epinephrine and/or phenylephrine. Doses can be titrated to the desired effect, keeping the doses ≤ 0.05 μg/kg/min for norepinephrine and epinephrine.

Blood pressure targets in case of hypertension: The threshold for systolic blood pressure (SBP) >160 mm Hg and/or MAP > 90 mm Hg. The pressures may be controlled by infusions of sodium nitroprusside 0.5–5.0 μg/kg/min or esmolol 100–500 μg/kg bolus followed by 100–300 μg/kg/min.

If the hemodynamic goals are not being met with the vasopressor and inotropic agents, hormone replacement therapy should be started. A combination of triiodothyronine- 4.0 μg bolus followed by 3.0 μg/hr. infusion or thyroxin 20 μg bolus + 10 μg/hr. infusion along with methylprednisolone 15 mg/kg bolus, repeated in 24 hours and vasopressin 1 unit bolus followed by an infusion 0.5–4.0 U/hr. A glucose insulin infusion (insulin bolus of 10 units in 50% dextrose) should be given to maintain blood glucose around 140 mg/dL. Attempts should be made to achieve the targets and maintain stability and identifying the organs suitable for procurement.

OTHER ISSUES IN BRAIN-DEAD PATIENTS

Diabetes Insipidus: It should be treated with continuous IV infusion of vasopressin (2.4U/hr.) or intermittent intravenous DDAVP. If needed, DDAVP can be used as a supplement to vasopressin. DDAVP should not be discontinued before shifting the patient to the OR.

Hypernatremia: Sodium levels above 150 mmol/L should be aggressively treated, as high levels are associated with significant graft loss.

Methylprednisolone: All donors should be given a dose of 15 mg/kg every 24 hours after neurological determination of brainstem death.

A hemoglobin level of 9–10 g/dL is appropriate in hemodynamically unstable patients; stable patients can tolerate upto 7g/dL levels. There are no defined targets for platelets or prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR). Fresh frozen plasma is indicated only for clinical bleeding. All blood samples for donor serology and tissue typing should be done before any transfusion is given. An initial base line blood cultures should be carried out in all donors and repeated after 24 hours and then as per the need. Antibiotics should be given for proven or suspected infection. Empiric broad-spectrum antibiotics are not indicated in donors.

Cardiac evaluation in cardiac donors: As suggested above, if LVEF is < 40%, a pulmonary artery catheter should be

by mansdocs.com

inserted and all required targets should be met. Troponin levels (either T or I) should be monitored every 12 hours as a standard monitoring. However, coronary angiography is indicated: maleb > 55 years or females > 60 years or males > 40 years and females > 45 years with two risk factors, presence of 3 or more risk factors at any age, history of cocaine use. If cath lab facilities are available, an angiogram must always be done to document coronary anatomy to help in decision making. In the absence of coronary angiography, cardiac donor organ suitability can be considered in the following circumstances: LVEF > 40% on 2D ECHO or hemodynamic stability or surgical inspection at the time of procurement.

Lungs and respiratory failure: There should be no lowest P/F ratio as criteria for organ suitability. Pulmonary hygiene can be maintained with positional therapy with lateral rotation every 2 hours, routine suction and physiotherapy to prevent atelectasis. Goals of mechanical ventilation: FIO_2 0.4, PaO_2 >100 mm Hg or oxygen saturation > 95%, $PaCO_2$ 35–40 mm Hg, arterial ph 7.35–7.45, tidal volume 8–10 mL/kg of predicted body weight, positive end-expiratory pressure (PEEP) 5 cm H_2O, plateau pressure < 30 cm H_2O. Bronchoscopy may be done as usual and the findings may be reported to the transplant surgeon. The aim of bronchoscopy is to evaluate anatomy, assess for foreign body and assist in its removal, define and locate aspirated material, secretions or apparent infection and clearance of secretions. Empiric antibiotics should be reserved only for patients with high risk of bronchopneumonia.

Suitability of donor liver: There are no upper limits of aspartate transaminase (AST), alanine transaminase (ALT) that precludes transplantation. All livers should be offered and the decision depends on organ status, trend of liver functions and recipient status. There is no mandatory requirement of a liver ultrasound in the prospective donors. The need for a liver biopsy should be discussed with the liver transplant team and is generally indicated for patients with weight > 100 kg or BMI > 30 or hepatitis C virus antibodies (HCVAb) positive donor. If biopsy cannot be done, liver should be offered and transplantation should be at the discretion of the liver transplant team.

Renal issues: Creatinine clearance should be done using Cockcroft- Gault equation and renal ultrasound may be done on a case-to-case basis. Kidney biopsy is not routinely indicated but may be reserved for age > 65 years or younger patients with creatinine level > 133µmol/L or hypertension or diabetes or abnormal urinalysis.

Organ functions must be optimized before procurement and it can be done in 12–24 hours with frequent reassessment of organ function towards defined targets. Once organ stability is achieved, before proceeding for donor organ retrieval, it must be ensured that valid consent has been taken for all the organs; necessary legal and regulatory requirements have been fulfilled. Ultimate decision about transplantation rests with the multidisciplinary transplantation team.

Post-organ retrieval, standard procedures and death protocols should be followed and any religious wish of the relatives may be considered sympathetically.

BIBLIOGRAPHY

1. Care of potential organ donor. NEJM. 2004;351:2730-9.
2. Organ donor management in Canada: recommendations of the forum on Medical Management to Optimize Donor Organ Potential. CMAJ. 2006;174(6);S13-30.
3. Organ donor problems and their management. Indian J Crit Care Med. 2006:10:21-34.

by mansdocs.com

CHAPTER

10

Scoring Systems in ICU

Avijatri Datta, Arindam Kar, Sauren Panja

SCORING SYSTEMS IN ICU

Scoring systems came into existence around 1980 as an objective tool which can be used to judge patient's condition and likely outcome. Scoring systems involve collection of data regarding a patient based on clinical and laboratory records; these collected data variables are assigned points. In order to obtain an overall score, these points are summated and adjusted with different weightage. Univariate analysis and multivariate statistical analysis are done and a predicted probability of outcome is obtained from an overall score against a large database of comparable patients. It is of outmost importance that the scoring system must be validated with independent data (that is on a population of patients independent from those used to develop the scoring system).

The scoring systems are particularly helpful for:

- assessing intensive care unit (ICU) performance and quality improvement
- predicting and planning ICU resource utilization
- Clinical research.

DIFFERENT ICU SCORING SYSTEMS

Many ICU scoring systems have been developed, it includes:

- APACHE (acute physiology and chronic health evaluation score)
- SAPS (simplified acute physiology score)
- MPM (mortality prediction model)
- SOFA (sequential organ failure assessment)
- MODS (multiple organ dysfunction score)
- LOD (logistic organ dysfunction model)
- TRIOS (three-day recalibrating ICU outcome).

For some systems, data are collected on first ICU day while some other systems involve data collection everyday throughout the ICU stay or first 3 days.

EVOLUTION OF DIFFERENT SCORING SYSTEMS

Acute Physiology and Chronic Health Evaluation (Table 1)

- APACHE II was developed from data on 5,815 medical and surgical patients at 13 hospitals in early eighties. Severity of illness was assessed with 12 routine physiologic measurements plus patient's age and previous health status with a maximum score of 71. It was seen that actual mortality was the same as predicted mortality only for patients directly admitted from emergency department. The mortality rate was higher than predicted for transfer for hospital floors, step-down units or other hospitals. APACHE III was published in 1991 and it addressed the limitations including the impact of treatment time and source of admission. The number of separate disease categories was increased from 45 to 78. Compared to APACHE II, the ranges of physiologic normal are narrower in APACHE III and deviations are asymmetrically weighed to be more clinically relevant. Interactions between variables were considered and five new variables (BUN, urine output, serum albumin, bilirubin and glucose) were added. Information also collected on 34 chronic health conditions of which seven (AIDS, hepatic failure, lymphoma, solid tumor with metastasis, leukemia/multiple myeloma, immunocompromised state and cirrhosis) were significant

by mansdocs.com

Table 1: APACHE II scoring system.

A. Acute physiological score

	APACHE II scoring system								
Variable	4	3	2	1	0	1	2	3	4
Temperature	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
Mean arterial BP	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate	≥50	35–49		25–34	Dec-24	10-Nov	06-Sep		≤5
(A-a)DO_2 (if FiO_2 > 50%)	≥500	350–499	200–3491		<20				
PaO_2 (if FiO_2 < 50%)					<70	61–70		55–60	≤55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
*Serum HCO_3	≥52	41–51.9		32–40.9	23–31.9		18–21.9	15–17.9	<15
Serum Na^+	≥180	160–176	155–159	150–154	130–149		120–129	111–119	≤110
Serum K^+	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine	≥3.5	2–3.4	1.5–1.9		0.6–1.4		< 0.6		
Hematocrit	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Glasgow Coma Score	Score = 15 - Actual GCS								

(WBC: White blood cell).

B. Age adjustment

Age (Yrs)	*Points*
<44	0
45–54	2
55–64	3
65–74	5
>75	6

C. Chronic health adjustment

Points can be added if the patient has a history of the following:

1. Biopsy-proven cirrhosis
2. New York Heart Association Class IV
3. Severe COPD (e.g. hypercapnia, home O_2, pulmonary hypertension)
4. Chronic dialysis
5. Immunocompromised

If any of above is present, add two points for elective surgery or for nonsurgical patients. Add five points for emergency surgery.

Total APACHE II = A ( ) + BC ( )+ C ( ) =

(APACHE: Acute physiology and chronic health evaluation; FiO_2: Fraction of Inspired Oxygen; (A-a)DO_2: Alveolar-arterial oxygen pressure difference; PaO_2: Partial pressure of oxygen; BP: Blood pressure; WBC: White blood cell; COPD: Chronic obstructive pulmonary disease; GCS: Glasgow Coma Score; ABG: Arterial blood gas).

*Use only if no ABGs.

in predicting outcome. APACHE III score ranges from 0 to 299 and a five-point increase indicates a significant increase in hospital death. In addition to APACHE III score which provides an initial risk estimate, there is an APACHE III predictive equation that uses the proprietary reference data on disease category and treatment location before ICU admission to provide individual risk estimate for ICU patients. APACHE IV was published in 2006 which included variables many of which were rescaled or revised compared

by mansdocs.com

with APACHE III. APACHE IV had excellent discrimination [receives operating characteristic (ROC) area = 0.88] and impressive calibration with a sample size of 110,588 patients in United States. APACHE IV relies on physiologic abnormalities to account for 66% of model's explanatory power, ICU admission diagnosis (116 categories) accounts for 17% with the remained accounted for by age, chronic illness and location prior to admission and interaction terms. But it also has its limitations—firstly the model is complex, secondly it was developed and validated in ICUs in the US and international differences in ICU resources, triage policies, models of care and bed availability would obviously have an impact on benchmarking performance in a new environment. APACHE IV produces a prediction once the patient is in ICU for 4 hours. If the patient should die even before 24-hour admission window, the prediction and outcome are still counted.

Simplified Acute Physiology Score

Simplified acute physiology score was developed on a population of 679 consecutive patients admitted to eight multidisciplinary ICUs in France. SAPS II was developed on 13,152 patients at 137 adult medical and surgical ICUs in Europe and North America sharing MPM II data set. Inclusion and exclusion criteria similar to APACHE. The outcome measure of SAPS II is vital status on hospital discharge. Seventeen variables were used in SAPS II model—12 physiological variables, age, type of admission and presence of AIDS, metastatic cancer and hematologic malignancy. SAPS III data were collected on 19,577 patients from 307 ICUs during 2002. Data were collected at admission, ICU days 1, 2, 3 and the last day of ICU stay. SAPS II when applied to this cohort underestimated hospital mortality, it discriminated well (ROC area 0.83), calibration was poor, model performance also differed by geographic region. The final SAPS III model created on 16,784 patients using logistic regression methods contains 20 variables, good discrimination (ROC area 0.848) and calibration.

Mortality Prediction Model

The original MPM model was developed on 755 patients in a single hospital using multiple logistic regressions to assign weights to variables predicting hospital mortality. MPM II models were developed on an international sample of 12,610 patients and then validated on a subsequent sample of 6,514. Exclusion criteria similar to APACHE. MPM puts more weight on chronic illness, comorbidities, age and less on acute physiologic derangement compared to APACHE. MPM models can use data obtained at ICU admission (MPM0) and also at the end of first 24-hour period (MPM24). MPM directly calculated probable of survival from available data, because it involves a logistic regression equation difficult to accomplish at bedside without a computer or programmable calculator.

The line of reasoning has been further extended to create 48-hour and 72-hour models. Probability of death increases at 48 and 72 hours even if the MPM variables and coefficients are unchanged implying mortality risk is increasing in patients whose clinical profile remains unchanged over time. The most important difference between MPM and other systems is that the MPM0 produces a probability estimate that is available at ICU presentation and independent of ICU treatment. MPM does not require specifying a diagnosis, which can be an advantage in complex ICU patients but it makes the model susceptible to error and generates a lower area under ROC curve. MPM III came into existence as all 15 variables from MPM0 II remained associated with mortality, but the relative impact has changed. Two new variables were added: (i) "full code" resuscitation status at ICU admission and (ii) "zero factor" or absence of all MPM0 II risk factors except age. Seven age interaction terms were added to reflect the declining marginal contribution of acute and chronic medical conditions to mortality risk in elderly; location and time prior to ICU admission were also evaluated. With these changes, MPM0 III calibrated well and had an area under ROC curve of 0.823.

Sequential Organ Failure Assessment (Table 2)

Sequential organ failure assessment (SOFA) system was created in a consensus meeting of the European Society of Intensive Care Medicine in 1994 and further revised in 1996. The SOFA is a six-organ dysfunction/failure score measuring multiple organ failure daily. Each organ is graded from 0 (normal) to 4 (the most abnormal), providing a daily score of 0–24 points. The objective in the development of the SOFA was to create a simple, reliable, and continuous score easily obtained in every institution. Sequential assessment of organ dysfunction during the first few days of ICU admission is a good indicator of prognosis. Both the mean and highest SOFA scores are particularly useful predictors of outcome. Independent of the initial score, an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%.

by mansdocs.com

Table 2: The sequential organ failure assessment.

	0	1	2	3	4
Respiratory: PO_2/FiO_2 ratio (mm Hg)	>400	≤400	≤300	≤200[b]	≤100[b]
Renal: Creatinine (mg/dL) or urine output	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500 mL/d	≥5.0 or < 200 mL/d
Hepatic: Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥12.0
Cardiovascular: Hypotension	No hypotension	MAP (<70 mmHg)	Dopamine (≤5) or dobutamine (any dose)[a]	Dopamine (>5) or epinephrine (≤0.1) or norepinephrine (≤0.1)[a]	Dopamine (>15) or epinephrine (>0.1) or norepinephrine (>0.1[a])
Hematologic: Platelet count ($\times 10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Neurologic: Glasgow Coma Score	15	13–14	10–12	6–9	<6

[a]Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/min)
[b]With ventilatory support.
(MAP: Mean arterial pressure; FiO_2: Fraction of inspired oxygen; PO_2: Partial pressure of oxygen).

Table 3: The multiple organ dysfunction score (PAR rate calculated as the product of the heart rate multiplied by the ratio of the right atrial pressure to the mean arterial pressure).

Organ system	*Score*				
	0	1	2	3	4
Respiratory: PO_2/FIO_2 ratio (mmHg)	>300	226–300	151–225	76–150	≤75
Renal: Serum creatinine (mg/dL)	≤1.1	1.2–2.2	2.3–3.9	4–5.6	≥5.7
Hepatic: Serum bilirubin (mg/dL)	≤1.2	1.3–3.5	3.6–7	7–14	>14
Cardiovascular: PAR	≤10	10.1–15	15.1–20	20.1–30	>30
Hematologic: Platelet count ($\times 10^3/mm^3$)	>120	81–120	51–80	21–50	≤20
Neurologic: Glasgow Coma Score	15	13–14	10–12	7–9	≤6

(PO_2: Partial pressure of oxygen; FiO_2: Fraction of inspired oxygen; PAR: Pressure adjusted heart rate).

Multiple Organ Dysfunction Score (Table 3)

The MODS was developed as a physiology-based tool to describe organ dysfunction as an ICU outcome. In 1995, Marshall examined the definitional criteria of organ failures and proposed and tested these criteria in a population of 692 patients. It was shown that mortality not only depends on admission but also on course.

Logistic Organ Dysfunction Model

This model, LOD, is based on logistic regression. From a European North American Database, 12 variables, were tested and organ failures defined. In this model, each dysfunction is given a weight of 0–5 points. Organ dysfunction included neurological, cardiovascular, renal, respiratory and hepatic failure. The difference between the LOD scores on day 3 and day 1 is highly predictive of hospital outcome.

Three-day Recalibrated ICU Outcome Score

A composite score using daily SAPS II AND LOD score for predicting hospital mortality in ICU patients hospitalized for more than 72 hours was proposed by Timsit et al. in 2001. This TRIOS composite score has excellent statistical qualities and may be used for research purposes.

COMPARISON BETWEEN MODELS (APACHE VS MPM VS SAPS)

In a retrospective chart review of 11,300 patients in the California Intensive Care Outcomes (CALICO) project, standardized mortality ratios (SMRs) were calculated using APACHE IV, MPM0 III, SAPS II. All models had adequate discrimination (typically by ROC curve area) and calibration (typically by goodness-of-fit procedures/ Hosmer-Lemeshow statistics). Substantial variation occurred in ICU risk adjusted mortality rates between ICUs

by mansdocs.com

regardless of the model used. The authors concluded, APACHE IV offers the best predicted accuracy with unlimited resources and that MPM0 III offers a viable alternative without a substantial loss in accuracy. Performance of three models based on 24-hour data (APACHE II, APACHE III, SAPS II) was compared to three models based on admission data (MPM II, SAPS II, SAPS III using Australian coefficients) for 1,741 patients in urban Australia showed no advantage in using 24-hour data versus data available at admission. Moreno and Morais compared performance of APACHE II with SAPS II in an independent database of 1,094 patients in 19 Portuguese ICU. Discrimination by ROC analysis was better with SAPS II but neither model calibrated well. In comparison of APACHE systems in 1,144 British ICU patients, APACHE II had better calibration but APACHE III has better discrimination. There have been no comparisons of the newest models (APACHE IV, MPM0 III, and SAPS III) on a large independent database. APACHE, MPM, SAPS are highly developed, prospectively validated tools useful for comparison for ICU performance in care of group of patients. Important implementation considerations include careful data collections, appropriate matching of models and the population under study and use of proper sample size and confidence intervals (CI) in reporting results. None of the models can perfectly predict the outcome of an individual patient. However, this limitation is true for any test utilized in medicine and need not preclude the use of prognostic estimates for clinical decision support. Physicians must be alert to limitations to severity-adjustment models in performance-based assessment, because case-mix differences, inadequate sample sizes or systemic errors in data collection can generate erroneous conclusions about quality of care. Outcomes are predicted for groups not individuals. Mortality probability ranges from 0.0 to 1.0, but an individual will either live or die. Use of scoring system to direct therapeutic choices has not been adequately studied.

STEPS INVOLVED IN DEVELOPING A SCORING SYSTEM MODEL

- *Precisely define outcomes of interest*: In any severity of illness or scoring system model, it is of paramount importance to define the outcome you are looking for.
- *Identify and define candidate predictor variables (data analysis, expert opinion)*: Presence of a large set of candidate predictor variables poses a problem. It is important to choose a small subset from the larger set so that the regression model has good predictive ability.
- *Examine continuous variables*: The purpose of such analyses is to assess whether the two variables are associated and to enable the value of one variable predicted from any known value of the other variable. (in order to assess response and to predict what the response would be).
- *Perform univariate analysis*: Univariate analysis usually refers to one predictor variable and one outcome variable. This can be done through various statistical methods including chi-square, Student's t-test, Fisher's exact, etc.
- *Perform multivariate analysis*: Multivariate analysis usually refers to more than one predictor variable or more than one outcome variable being evaluated simultaneously. This can be done through various statistical methods including logistic regression, linear regression, neural nets, Bayesian, etc.
- *Examine and adjust for interaction between variables*: When two or more independent variables are involved, the effect of one independent variable on the dependent variable of interest may not be the same at all levels of the other independent variable or the effect of one independent variable may depend on the level of the other independent variable. In order to find an interaction, you must have a design, in which the two (or more) independent variables are "crossed" with one another so that there are observations at every combination of levels of the two independent variables.
- Develop score or equation that relates independent variables to outcome.
- *Test calibration of model*: Calibration evaluates the degree of correspondence between the estimated probabilities of mortality produced by a model and actual mortality experienced by the patients. Calibration can be statistically evaluated with goodness-of-fit tests. In order to test calibration, patients are rank-ordered according to their probability of mortality and grouped into range defined strata. Typically, 10 such stratums are formed, to predict numbers of deaths in the strata, the probabilities of mortality for all patients in the stratum are summed. Formal goodness-of-fit testing compares the observed with the predicted numbers of death and the observed with the predicted numbers of survivors in each stratum of patients. It is necessary to assess the value obtained to decide whether the discrepancy between observed and predicted outcome across all strata is within sampling variability. If differences are large, the model does not calibrate adequately and the outcome reflection is not proper.

by mansdocs.com

- *Test discrimination of model (ROC area C-statistic, sensitivity and specificity)*: Discrimination uses the area under the ROC curve, in order to evaluate whether the model chosen is able to distinguish patients who die from patients who live, based on estimated probabilities of mortality. For a ROC curve, sequence of probability cut off points is specified. A 2 × 2 classification table of predicted and observed outcome is constructed for each cutoff. Observed mortality is noted for each patient, and from the table, true-positive and false-positive rates are determined. These pairs of rates for the sequence of cutoff points are plotted, resulting in the ROC curve. The higher the true-positive rate in relative to false-positive rate, the greater is the area under the ROC curve. Good test approach, the top left corner of the curve with ROC area of model, exceeds 0.70.
- Validate model with independent data, split sample or jackknife techniques.
- Obtain external validation in new setting and customize as needed.
- Publish in peer review journal.

PRACTICAL USE OF APACHE IV IN A MULTIDISCIPLINARY ICU TO EVALUATE OUTCOME

Scoring systems were introduced to critical care to provide an objective tool for judging the patient's condition and likely outcome. It can also be used to estimate the severity of illness and likely to aid therapeutic decisions. Through scoring systems prediction of individual outcome of ICU patients cannot be done adequately, but these validated models may prognosticate groups of patients with similar presentation of illness. The use of scoring systems to predict risk of mortality and evaluating outcome in critically ill patients is very important. Several severity-based scoring systems are in place of which APACHE scoring system is one of the most commonly used in ICUs all over the world. APACHE takes into account various considerations including physiological variables, vital signs, urine output, neurological score, age-related parameters and comorbid conditions all of which may have a significant impact on outcome.

The authors conducted a prospective study in a multidisciplinary ICU in Eastern India to determine the value of scoring systems in predicting outcome in their case-mix. APACHE IV model was used to assess the outcome. All 962 patients consecutively admitted over a period of 1 year (January 2013 to December 2013) to the author's ICU were included in the study. The patients who were readmitted during the same period were excluded. The day after ICU admission, the worst values on APACHE IV during 24 hours following ICU admission were taken and APACHE scores were calculated using online APACHE score calculator. Observed mortality rates were compared with predicted mortality and SMR with 95% CI, sensitivity and specificity determined. The median age was 62 years. The APACHE IV scores ranged between 4 and 179 and median APACHE IV score was 56. The mean APACHE IV score of non-survivors was significantly higher (96.93 ± 35.15) compared to that of survivors (50.59 ± 23.06) (p-value < 0.0001). The observed mortality in all patients was 22.66% (218 cases), while APACHE IV predicted mortality was 22.46% (216.06 cases) with a SMR of 1.008.

PITFALLS IN APPLICATION OF SCORING SYSTEMS

- *Data collection and entry errors*: Ensure that data input is performed in a timely manner by authorized and qualified staff. Correction and resubmission of data that were erroneously input should be performed without compromising original transaction authorization levels. Apart from improper data collection, there can be sampling or non-sampling error. It is important to be aware of these errors, in particular non-sampling errors, so that they can be either minimized or eliminated from the data collected.
- *Misapplications of the model*: Different scoring systems have been developed over years and they have a pivotal role in ICU care. While applying these scoring systems, it is vital to ascertain factors that can influence their performance so that the application is fair and appropriate. All scoring systems have its limitations, even in case of a high score, it is important to analyze how those scores were developed and generated, and how and when the raw patient data were collected.
- *Confidence interval not reported*: P values and CI are reported in almost all scientific writings and are used in interpreting results. The reporting of p values and CI usually follows hypothesis testing or significance testing. Most scientific investigations involve the testing of hypotheses. These are formal procedures for testing whether findings from the investigations are compatible with a so called null hypothesis. Hypotheses refer

by mansdocs.com

to statements concerning the situation being investigated which are usually stated as two mutually exclusive options: a null hypothesis and an alternative hypothesis. The null hypothesis is a statement of no association between variables or no difference in means of groups while the alternative hypothesis states that there is a difference or an association. The CI gives the range of values within which we are reasonably confident that the population parameter lies. The parameter here could be difference in means or proportions of two groups or it could be a measure of association between two variables. The most commonly reported interval is the 95% CI.

- *Computational errors*: Personal computers, spread sheets, professional statistical packages, and other information technologies are now ubiquitous in statistical data analysis. Without using these tools, one cannot perform any realistic statistical data analysis on large data sets. To perform for statistical data analysis, the online statistical calculators such as excel have three major problems: (i) they are slow, (ii) they depend on the cyberspace connection and (iii) the more serious problem is that they are very limited. Statistical analysis system (SAS) is a widely used and powerful tool for data analysis with excellent data management capabilities.
- *Failure to account for sample size*: Sample size determination is the act of choosing the number of observations or replicates to include in a statistical sample. The sample size is an important feature of any empirical study in which the goal is to make inferences about a population from a sample. In practice, the sample size used in a study is determined based on the expense of data collection, and the need to have sufficient statistical power. In complicated studies, there may be several different sample sizes involved in the study. A too large sample size may lead to the rejection of a null hypothesis even if the actual effect is so small, that it does not have practical importance.
- *Chance variability*: "Chance variation" or "chance error" or "random error" is the inherent error in any predictive statistical model. It is defined as the difference between the predicted value of a variable (by the statistical model in question) and the actual value of the variable. For a fairly large sample size, these errors are seen to be uniformly distributed above and below the mean and cancel each other out, resulting in an expected value of zero.
- *Determination of diagnosis prone to bias*: Concern is that subjects have different probability of being selected according to exposures or outcomes of interest, creating a biased measure of association (i.e. odds ratio, relative risk). A biased study loses its validity with respect to the degree of bias.
- *Lead time bias (pre ICU stabilization)*: Lead time bias is the bias that occurs when two tests for a disease are compared, and one test (pre-ICU stabilization) diagnoses the disease earlier, but there is no effect on the outcome of the disease—it may appear that the test prolonged survival, when in fact it only resulted in earlier diagnosis when compared to traditional methods. It is an important factor when evaluating the effectiveness of a specific test.
- *Inclusion of ineligible patients*: Eligibility errors can be avoided by careful scrutiny before random allocation. Allocation of ineligible patients should be avoided.
- *Wrong diagnosis selected*: The importance of accuracy in coding cannot be underestimated as wrong coding or diagnosis will severely affect the effectiveness of the scoring system.
- Deliberate gaming of the system.

CONCLUSION

Severity illness scoring systems such as APACHE/SAPS/MPM have become important tools for the evaluation and planning of intensive care practice patterns. They are objective tools used as a group measurement for patients with similar disease process; however, they are not suited for individual use. These systems and tools provide greater degree of accuracy and precision essential for benchmarking. There has been extensive literature and studies related to advance in technical aspects of scoring systems.

Regular calibrations of these scoring systems to more contemporary cohorts are now recommended. Poor model performance in diagnostic subgroups have led to the evolution of existing scores into a third and fourth generations of illness severity scoring systems, such as SAPS III and APACHE III and IV. These evolutions involved addition of new variables, new statistical methods and diagnostic groups or subgroups with change to measurement of certain physiological and diagnostic variables. The calibration (of these newer systems) with more contemporary cohorts make these changes more externally valid in terms of case-mix and also take into consideration the clinical information that was not initially taken

by mansdocs.com

during development of earlier systems. There is a widespread move amongst ICUs to this newer generation of illness scoring systems, although their performance is only marginally better than earlier versions of the scores that have been more simply recalibrated by reestimating coefficients. Efforts are on to find new methods to assess ICU performance for future.

BIBLIOGRAPHY

1. Angus DC, Sirio CA, Clermont G, et al. International comparisons of critical care outcome and resource consumption. Crit Care Clin. 1997;13(2):389-407.
2. Bastos PG, Sun X, Wagner DP, et al. Application of the APACHE III prognostic system in Brazilian intensive care units: a prospective multicenter study. Intensive Care Med. 1996;22(6):564-70.
3. Beck DH, Taylor BL, Millar B, et al. Prediction of outcome from intensive care: a prospective cohort study comparing acute physiology and chronic health evaluation II and III prognostic scores in a United Kingdom intensive care unit. Crit Care Med. 1997;25(1):9-15.
4. Becker RB, Zimmerman JE. ICU scoring systems allow prediction of patient outcomes or comparison of ICU performance. Crit Care Clin. 1996;12(3):503-14.
5. Berger MM, Marazzi A, Freeman J, et al. Evaluation of the consistency of Acute Physiology and Chronic Health Evaluation (APACHE II) scoring in a surgical intensive care unit. Crit Care Med. 1992;20(12):1681-7.
6. Cerra FB, Negro F, Abrams J. APACHE II score does not predict multiple organ failure or mortality in postoperative surgical patients. Arch Surg. 1990;125(4):519-22.
7. Forrest CB, Shipman SA, Dougherty D, et al. Outcomes research in pediatric settings: recent trends and future directions. Pediatrics. 2003;111(1):171-8.
8. Hariharan S, Moseley HS, Kumar AY, et al. Futility-of-care decisions in the treatment of moribund intensive care patients in a developing country. Can J Anesth. 2003;50(8):847-52.
9. Hariharan S, Moseley HSL, Kumar AY. Outcome evaluation in a surgical intensive care unit in Barbados. Anaesthesia. 2002;57(5):434-41.
10. Jean-Roger Le Gall. The use of severity scores in the intensive care unit. Intensive Care Med. 2005;31:1618-23.
11. Katsaragakis S, Papadimitropoulos K, Antonakis P, et al. Comparison of Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) scoring systems in a single Greek intensive care unit. Crit Care Med. 2000;28(2):426-32.
12. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
13. Marik PE, Varon J. Severity scoring and outcome assessment: computerized predictive models and scoring systems. Crit Care Clin. 1999;15(3):633-46.
14. Muckart DJ, Bhagwanjee S, Gouws E. Validation of an outcome prediction model for critically ill trauma patients without head injury. J Trauma. 1997;43(6):934-8.
15. Oh TE, Hutchinson R, Short S, et al. Verification of the acute physiology and chronic health evaluation scoring system in a Hong Kong intensive care unit. Crit Care Med. 1993;21(5):698-705.
16. Ozer EA, Kizilgunesler A, Sarioglu B, et al. The Comparison of PRISM and PIM scoring systems for mortality risk in infantile intensive care. J Trop Pediatr. 2004;50(6):334-8.
17. Rogers J, Fuller HD. Use of Acute Physiology and Chronic Health evaluation (APACHE II) scores to predict individual patient survival rate. Crit Care Med. 1994;22(9):1402-5.
18. Rosenberg AL, Zimmerman JE, Alzola C, et al. Intensive care unit length of stay: recent changes and future challenges. Crit Care Med. 2000;28(10):3465-73.
19. Rowan KM, Kerr JH, McPherson K, et al. Intensive Care Society's APACHE II study in Britain and Ireland. I. Variations ion case mix of adult admissions to general intensive care units and impact on outcome. BMJ. 1993;307:972-6.
20. Rowan KM, Kerr JH, McPherson K, et al. Intensive Care Society's APACHE II study in Britain and Ireland. II. Outcome comparisons of intensive care units often adjusted for case mix by American APACHE II method. BMJ. 1993;307:977-81.
21. Sachdeva RC, Guntupalli KK. International comparisons of outcomes in intensive care units. Crit Care Med. 1999;27(9):2032-3.
22. Shann F, Pearson G, Slater A, et al. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Intensive Care Med. 1997;23:201-7.
23. Sirio CA, Tajimi K, Tase C, et al. An initial comparison of intensive care in Japan and the United States. Crit Care Med. 1992;20(9):1207-15.
24. Slater A, Shann F, Pearson G. Paediatric index of mortality (PIM) Study Group. PIM 2: a revised version of the paediatric index of mortality. Intensive Care Med. 2003;29:278-85.
25. Tibby S, Taylor D, Festa M, et al. A comparison of three scoring systems for mortality risk among retrieved intensive care patients. Arch Dis Child. 2002;87(5):421-5.
26. van Keulen JG, Polderman KH, Gemke RJ. Reliability of PRISM and PIM scores in paediatric intensive care. Arch Dis Child. 2005;90(2):211-4.
27. Wong DT, Crofts SL, Gomez M, et al. Evaluation of predictive ability of APACHE II system and hospital outcome in Canadian intensive care patients. Crit Care Med. 1995;23(7):1177-83.
28. Zimmerman JE. Measuring intensive care performance: a way to move forward. Crit Care Med. 2002; 30(9):2149-50.

by mansdocs.com

CHAPTER

11

Guidelines for ICU Planning and Designing in India

Narendra Rungta, Neena Rungta, Manish Munjal, Neeru Gaur, Anamika Chaudhary

INTRODUCTION

In India the scenario of development of critical care unit is fast catching up and the concept of intensive care units (ICUs) has gained widespread acceptance with tremendous increase in the knowledge, technology, skills and active participation of all multispecialty. ICU is complex, specifically designed, staffed, located and fully equipped, dedicated to management of critically sick patients and it should include both clinically oriented and design-based multiprofessional team members who prove the "*Mission To Save Lives With The Vision Of Excellence*". Expertization in this separate specialty along with additional facilities and improved care reduced the morbidity, and mortality in ICU. That is why an optimum ICU design and periodic modifications requires the regulatory agency standards and expertize of critical care practitioners along with multidisciplinary approaches with expertization necessary to treat them. It operates with defined policies, protocols, and procedures and has its own quality control, education, training and research programs. ICU designing guidelines should be good for both rural and urban areas as well as smaller or tertiary care management in hospital as the changes in model of care delivery may drive ICU design. Due to global nature of intensive care, these guidelines were written and updated with the intent to be used by health care organizations around the world.

Need for a New ICU/Renovation of the Old One

Some issues are changing so rapidly, such as information technology, patient demographics, disease patterns, re-emerging of disease or emerging of the new disease with more severity and needs extra and new strategies of management. For that reason hospital should upgrade the ICU to accommodate the changes and accept inflow from everywhere with best possible and cost-effective care and with least rate of nosocomial infection.

Designing for infection control by separating the patients, adding isolation facilities, adding hand hygiene stations, upgrading mechanical ventilation and filtration, revising provision for disposal of human waste or introduction of antimicrobial materials can lower infection rate and therefore morbidity and mortality, cost per care, and length of stay.

Advances in technology have led to miniaturization of equipment and have increase the amount of equipment



Fig. 1: Panoramic view of the ICU.

by mansdocs.com



Fig. 2: A view of individual beds in the ICU.

needed. Optimum ICU design can help to reduce medical errors and improves patient outcomes and can play role in reducing the total bill of the patient and that is why the following areas should be taken care of before planning a fully equipped and functional ICU.

GOAL

"*A healing environment and mission to save life with a vision of excellence*".

It includes improvement in physical and psychological states of patient, staff, physicians and visitors by reducing noise levels, minimize glare and support infection control, floor plans, equipment, minimizing occupational injuries, stress reducing furnishings and décor incorporating natural light and view of nature.

ICU Planning

Development of functional programs are necessary for the actual ICU design to accomplish as the evidence based design gets benefit from ever changing experience of best practices of health care team members along with information technology.

- Initial planning
  - Team formation and leader/coordinator
  - Data collection and analysis
  - Beginning of the process and decide about budget allocation, aims, and objectives.
- Decision about ICU level, number of beds, design and future thoughts
  - Design for the future:
    - Designers must look to the long term. An effective design must be flexible enough to accommodate changing care practices and advances and technology over the unit's life span.

Table 1: Role of team members in ICU planning.

Team members	*Roles*
Hospital administration	Unit sizing based on utilization, finance and budget
Clinical team	Multi disciplinary group including physicians, nurses, infection control specialists, pharmacists, therapists and ancillary staff
Design team	The architect, engineers and technology planner (with Leadership in Energy and Environmental Design (LEED) certification-Leadership in Energy and Environmental Design)
Hospital services and representatives	Includes material management environmental services, food services, housekeeping staff, and other

CRITICAL CARE UNIT (CCU)—FUNCTIONAL MODEL

The CCU consists of four major zones each housing a primary function or set of interrelated functions.

Size and Arrangement of Critical Care Unit

The most current edition of FGI guidelines (SCCM) provide square footage (at least 100 sq ft/patient, ideally 125 sq ft/patient) requirement for selected room. Traditional design of critical care units have been influenced by single paper medical record central monitors and regulations promoting a single, centrally located work station from which all beds within the unit can be observed. These conditions are changing as information system allows digital records to be in multiple places at once, interdisciplinary care teams become more prevalent, nursing

by mansdocs.com

Table 2: Planning according to the level of ICU.

Level	*Recommendations*	*Beds*	*Functions*
I	Small district hospital, private nursing homes, rural centers	6–8 beds	• Handling emergencies • Resuscitation and cardiopulmonary resuscitation (CPR) • Ventilation at least for 24–48 hrs • Noninvasive monitoring • Basic lab investigations and imaging • At least one book of critical care medicine
II	Level I plus, large general hospitals	6–12 beds	• Lead by an intensivists • Multisystem life support • Invasive/noninvasive ventilation/monitoring • CPR, TC pacing • Follow protocols and policies • Fully equipped ICU and lab • Imaging including USG and CT • Strong microbiology support • Blood bank – own/outsourced • Research work are recommended • Supported by multispecialty doctors • Resident doctors must be updated for Fundamental Critical Care Support (FCCS), Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS)
III	Level II plus, tertiary level hospitals	10–16 beds one or multiple ICUs with multispecialty	• Preferably a closed ICU • Headed by intensivists • Protocols, policies and research are observed • Noninvasive/invasive/continuous hemodynamic monitoring • Intra/inter hospital transport facilities • Center for training ICU nurses/residents • Bedside imaging/USG/bronchoscopy, endoscopy, hemodialy sis, renal replacement therapy (RRT) • Care of infection control • Blood bank and laboratory • Optimum patient: nurse ratio 1:1 • Continuous up gradation of knowledge in critical care, seminars, journal clubs, mortality meets, case discussions among all specialty doctors and residents • Provision for organ donation, and end of life support

Table 3: Division of zones in the ICU.

	Zones	*Area*	*Functions*
1.	Patient care zone	Patient room and adjacent areas	Direct patient care
2.	Clinical support zone	Patient room as well as other areas of unit	Function closely related to patient care
3.	Unit support zone	Administrative, material management, laboratories, canteen and staff support areas	Administration, staff support function
4.	Family support zone	Reception, counseling room, help desk, retiring/ waiting room	Support families and visitors

moves closer to bedside, families become more involved in patient care, technology advances and functions that had been centralized become decentralized. Whether a centralized or decentralized design is chosen, caregivers must be able to observe patient from many points within the unit.

by mansdocs.com

Number of Beds and Number of ICU as Needed for the Institution

- The number of ICU depends on hospital data and future requirements
- The number of beds recommended in a hospital is usually 4 beds/100 hospital beds
- Minimum of 6 beds for reason of efficiency and economy, to a maximum of 8–12 beds for reason of observation. If there is need for more than 12 beds, consider arranging them in multiple pods.

ICU Bed Designing and Space Issues

- Space/bed: 125–50 sq ft.
- About 100–150% extra space to accommodate nursing station, equipment, storage, doctor's room, toilet, patient movement area with bedside X-ray, intubation, RRT, information communication distribution transaction (ICTD) and procedure facilities
- Ten percent of the total ICU beds for isolation room
- Two beds should have provision of RRT with water outlets nearby
- Planners should take care for accommodation of future advancement and technologies and modulation accordingly.

Nursing Station Designing and Planning

Location, space and facilities: This is the nerve center of the ICU and it is centrally located, and it has in charge nurse, doctors, IT/computer guy, machines, computer, scanners, printers, medicine stores, linen and ancillaries.

Design of Patient Care Zone

- *Single rooms*: Superiors to multi bedrooms and enhance privacy. Traditionally curtains are used to separate the patient beds. But single rooms are preferred by SCCM.
- *Clear floor areas*: The space not occupied by the patient, fixed room furnishings and equipment which allows bedside X-ray, USG, ECHO, RRT. It should be 4 ft at the head and foot end and 6 ft on each sides of patient's bed.
- *Medical utility distribution system*: The choice of system for mounting and organizing electrical, medical gas, vacuums and other medical utility outlets has a major impact on patient and staff satisfaction.
- *Doors*: These should be of adequate size for safe, easy and fast transport of critically sick patient, provide easy movement of patient bed and crash cart/trolley.
- *Windows*: Glass covered windows as the natural light with outside view is essential for the wellbeing of patient and staff.
- *Floor, walls and ceilings*:
  - Ceilings, floor should be easy to clean, non slippery tiles.
  - Walls with 4–5 ft finished tiles and color to create a comfortable environment for patient's healing.
- *Noise control in ICU*: Noise level monitors can be used.
- *Temperature control, heating, ventilation and air conditioning (HVAC) system*:
  - Temperature range is 16–25°C.
  - Fully air condition allows control of temperature, humidity and air change.



Figs 3A and B: Panoramic view of the ICU nursing station.

by mansdocs.com

Table 4: List of equipment.

S.No.	Name	Numbers
1.	Bedside multipara monitors with noninvasive and invasive monitoring ports and online accessibility	1/bed
2.	Ventilators both adults and pediatric and with graphics/loops view, updated with recent modes and modified according to future needs	6
3.	Noninvasive ventilators	3
4.	Infusion pumps	2/bed
5.	Syringe pump	2/bed
6.	Power columns and panels with multiutility plugs	1/bed
7.	Defibrillator with TCP facility	2
8.	ICU beds	1/patient
9.	Overbed tables	1/bed
10.	ABG machine	1
11.	Crash cart	2
12.	Freeze	1
13.	Microwave	1
14.	Computers, scanner and printer	1
15.	HD machines	2
16.	Continuous renal replacement therapy (CRRT)	1
17.	Leg compression machines	2
18.	Airbeds	6
19.	Laryngoscope	2
20.	Glucometer	2
21.	Bedside X-ray	1
22.	Spinal board	2
23.	ETO sterilization	1
24.	Rigid cervical collar	4
25.	Resuscitation face mask of different sizes (AMBU) mask with different sizes	10
26.	Buckets for waste disposal	Set of four for each bed
27.	Procedure trolley	2
28.	IA ballon pump	1
29.	Fiberoptic bronchoscope	1
30.	Stethoscope	1/bed
31.	ECG machine	1
32.	Endotracheal tubes	2 sets of all sizes
33.	Laryngeal mask airway (LMA) and i-gel	2 sets
34.	Telephone and ICU mobile	2
35.	PCT kit and chest drains	1

Table 5: Medical utility systems used in ICU.

Medical utility system	Usage
Flat head wall configuration	• Mounted on the wall at the head end of the bed • Widespread • Can create problems in crisis/code situations in managing the airway and multiple cords of i.v lines
Fixed power columns	• Has array of outlets on a non-movable vertical column attached to ceiling • Allows free movement
Boom configurations Ceiling/Pendant mounted	• Offer maximum flexibility, multiple outlets, brackets, poles and shelves for easy placement of monitors and accessories and reduce clutter on the floor • Pendant mounted boom configurations are the best for easy/immediate unrestricted access during the crises • Height of the monitoring system should be comfortable for staff and doctors • Bed should be 2 ft away from the head wall for making access in emergency immediately

Table 6: Recommendations for sound level in ICU.

Timings	Recommended noise levels
Daytime	< 45 dBA
Evening	40 dBA
Night	20 dBA

- *Lighting*:
  - Overhead lighting should be 20 ft candles.
  - Recommended spot light is 150 ft candles. And overall the natural light is helpful in staff and patient outcome.
- *Hand hygiene and prevention of infection*:
  - Every bed should have attached alcohol based antimicrobial instant hand wash solution, which should be used by caregivers (doctors/nurses/paramedical/relatives).
  - Water basins are not successful because of poor compliance and maintenance issues.
  - An operation room style sink with elbow and foot operated water supply system.
  - All entrants should wear cap and mask.

by mansdocs.com

- *Waste disposal*: It is mandatory to follow the government regulations strictly and four color coded disposal of waste.
- *Isolation* needed in case of immunocompromised patient, burn, etc.
- *Pet visitation* as given by SCCM.

CLINICAL SUPPORT ZONE

- Include all unit function related to diagnoses and treatment of patient. Careful analysis of workflow and patient care processes is needed to optimize design of clinical support zones.
- It includes emergency eyewash station, team work areas, physiologic monitoring, computer based order entry, documentation and review, pharmacy services, preparing and dispensing patient medication, laboratory, imaging, respiratory therapy, specialized procedure areas, emergency equipment and supplies- crash carts, non emergency equipment—specialty beds, stretchers, wheel chairs, isolation carts, traction devices, diagnostic equipment, care of patient nourishment and patient transportation.
- *Disaster preparedness*: Ready for managing disaster in the ICU as well as in the hospital. Provision alarms is a mandatory requirement in India now.

UNIT SUPPORT ZONE

- *Administrative functions*: Offices and conference facilities can be located in the administrative office complex which also has a conference room for conducting various training programs, seminars and meetings. The conference room should be equipped with telephone, wi-fi access, audiovisual equipment, teaching aides and has should have access to emergency announcements and codes. accessible through
- *Needs of doctors and nurses*: Staff support function—need changing/rest rooms and personnel lockers, doctor's room with intercom/emergency alarms, toilets. Duty room should be in close proximity to the unit, working table with internet connection in ICU.
- Security and access control—have video camera monitoring and card key access
- Safe guarding patient privacy and patient safety technology
- Support system recommendations of storage, communication and computer. Central communications should include information technology, tele-communication, bed-to-bed over, personnel tracking by numeric and color-coded symbols and document transmission
- Material management and housekeeping function by clean/soiled utility rooms and housekeeping which provide adequate waste disposal and cleanliness, materials and finishes.

Table 7: Recommendations for Indian ICUs for level I and II.

Basic requirement	*Number*
• Unit size	6–12 beds
• Bed space	Minimum 100 sq ft, desirable > 125 sq ft
• Additional space	100% extra of bed space
• Oxygen outlets	2
• Vacuum outlets	2
• Compressed air outlets	1
• Electrical outlets	12, of which 4 may be near the floor and 2 on each sides

FAMILY SUPPORT ZONE

- It is very important to value family members and take care of their needs
- It includes signage and wayfinding, family lounge, consultation rooms, meditation spaces, Family communications, family nourishment, family sleep rooms and family laundry.

HIGH DEPENDENCY UNIT

- It is the area where patient care level is intermediate between ICU and floors and usually located near the ICU complex and has staff almost similar to ICU and at least 50% of the main ICU
- Following types of patients may be kept here: Patient recovered from critical sickness, who are less sick like single organ failure not requiring invasive monitoring or invasive MV, patient requiring close observation that are strong suspects of getting deteriorated
- Doctor/patient ratio and nurse/patient ratio may be much more relaxed
- There are conflicting reports suggesting usefulness of such units. But in Indian circumstances and surveys indicate that HDU has helped in our circumstances. Possibly in following way by cutting cost of patient of health service provider requiring close observation and not needing ICU

by mansdocs.com

- Psychological relief to the family and patient that he is being observed meant for lesser sick patient
- It may be handy to public hospitals where there is always shortage of ICU beds.

SUMMARY

- ICU is a specialized part of a hospital or nursing home where very sick patient are treated.
- It should be located near ER or OT and easily accessible to clinical lab, imaging and operating rooms.
- Ideal bed strength should be 8–10.
- Each patient should have a room size of less than 100 sq ft, however a space of 125–150 sq ft will be desirable.
- Additional space equivalent to 100% of patient room area should be allocated to accommodate nursing station, shortage, etc.
- Ten percent beds should be reserved for patient requiring isolation.
- Two beds for patient undergoing renal replacement therapy (RRT).
- There should be at least two barriers to the entry of ICU.
- There should be only one entry and exit to ICU to allow free access to heavy duty machine like mobile X-ray, bed and trolleys on wheels.
- At some time it is essentials to have an emergency exit for rescue removal of patient in emergency and disaster situations.
- Proper fire fighting/extinguishing machines should be there.
- It is desirable to have access to natural light as much as possible to each patient.
- List of equipment and number of oxygen, vacuum, compressed air outlets are listed on the guidelines.
- Every ICU has qualified/trained intensivist as its leader.
- One doctor for five patients may ideal ratio.
- 1:1 patient-nurse ratio is ideal, but a minimum of 1:2 nurse patient ratio should be maintained for sick ventilated patients, who are being monitored invasively and require other supportive therapies like renal replacement therapy for sustaining life.
- Other personnel needed for ICU have been listed.
- ICU should practices given protocols on all given conditions.
- Requirement for furniture, storage, light, noise, flooring walls, ceiling air-conditioning, ventilation, etc have been described in guidelines in details.
- Needs for doctors, nurses, and relatives of patient should be carefully observed.

BIBLIOGRAPHY

1. American College of Critical Care Medicine's Taskforce on Guidelines: Guidelines for Intensive Care Unit Design. SCCM and AACN. 1993.
2. American Institute of Architects Committee on Architecture for Health and the U.S. Department of Health and Human Services—Guidelines for Construction and Equipment/Hospital and Medical Facilities. AIA Press, 1996.
3. Boots R, Lipman J. High dependency units: issues to consider in their planning. Anaesth Intensive Care. 2002;30(2): 348-54.
4. Byrick RJ, Mazer CD, Caskennette GM. Closure of an intermediate care unit: impact on critical care utilization. Chest. 1993;104(3):876-81.
5. Critical design and Furnishing – Edited by Maurine A Harvey SCCM 2001.
6. Dara SI, Afessa B. Intensivist-to-bed ratio: association with outcomes in the medical ICU. Chest. 2005;128(2):567-72.
7. Dara SI et al Intensive to bed ratio association with outcome ratio in Medical ICU.
8. Duffy TM, F1ore11, JM1CUs: An Integrated Approach to Design. Journal of Health Care Interior Design. 1990;II: I67-79.
9. Guidelines for Categorization of Services for the Critically ill Patient. Crit Care Med. 1991;19(21):279-85.
10. Guidelines for the Transport of Critically Ill Patients. Crit Care Med. 1993;21(6):931-47.
11. ICU Design Video: Compilation of 3-5 minute video tours and floor plans from the top entrants since 1992 for the ICU Design Citation.
12. Martin J et al – Intensive care resources and Activity: Australia and New Zealand 2003-2005 Melbourne ANZICS 2006.
13. Minimum standards for HDU – Policy document IC13 Melbourne,Joint faculty of Intensive Care Medicine, 2000.
14. Personal Survey Inference
15. Proposed Guidelines for ICUs in India - website Indian Society of Critical Care Medicine.
16. Recommendations for ICU Admission and Discharge Criteria. Crit Care Med. 1988;16(8):807-8.
17. Recommendations for Services and Personnel for Delivery of Care in Critical Care Settings. Crit Care Med. 1988:16(8): 809-11.
18. Society of Critical Care Medicine Guidelines for Intensive Care Unit Design (Guidelines/Practice + Committee of the American College of Critical Care Medicine Society of Critical Care Medicine) 1995.
19. Standards for intensive care Unit design prepared by Intensive Care Society 1995.
20. Thomsan DR, Hamilton DK, Cadenhead CD, et al. Guidelines for intensive care unit design. Crit Care Med. 2012;40 (5):1586-600.

by mansdocs.com

CHAPTER

12

Guidelines and Protocols in ICU

Manoj Singh, Mehul Solanki

INTRODUCTION

Clinical guidelines are systematically developed statements designed to help practitioners and patients decide on appropriate healthcare for specific clinical conditions/circumstances. They provide extensive, critical and well-balanced information on the benefits and limitations of various diagnostic and therapeutic interventions so that physician can carefully judge individual cases. The guidelines are mostly followed in clinical practice due to the way they are developed, implemented and monitored. Good guidelines can change clinical practice and influence patient outcome. If guidelines are to achieve their potential, they should have adequate resources and be introduced through partnerships that may include clinicians, providers, purchasers and the public. They are used in wide range of settings to promote effective and efficient healthcare, for example, to guide the introduction of new procedures or services, promote effective healthcare in primary or secondary settings, encourage the adoption of cost-effective interventions and improve the timing and processes of the discharge of patients.

HISTORICAL BACKGROUND OF CLINICAL PRACTICE AND GUIDELINES

460 BC	Oath of Hippocrates
1930s	US Food, Drugs and Cosmetic Act
1947	Nuremberg Code
Dec 10, 1948	Declaration of Human Rights
1962	Kefauver-Harris Amendment
1964, revised 2000	Declaration of Helsinki
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects
1996	International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines issued
1997	ICH-GCP guidelines become law in some countries.

DEFINING TERM

Guidelines

Guidelines reduce unacceptable or undesirable variations in practice and provide a focus for discussion among health professionals and patients. They enable professionals from different disciplines to come to an agreement about treatment and devise a quality framework, against which practice can be measured. Guidelines can help commissioners and purchasers to make informed decisions and provide managers with a useful framework for assessing treatment costs.

Protocols

Protocols are rigid statements allowing little or no flexibility or variation. A protocol sets out a precise sequence of activities to be adhered to in the management of a specific clinical condition. There is a logical sequence and precision of listed activities.

by mansdocs.com

GUIDELINES AND PROTOCOLS AVAILABLE IN INTENSIVE CARE FOR HEALTHCARE PROFESSIONALS

- Admission and discharge criteria
- Surviving sepsis
- Ventilator-associated pneumonia
- Central line-related blood-stream infection
- End of life care
- Acute respiratory distress syndrome/acute lung injury (ARDS/ALI)
- Cardiopulmonary resuscitation
- Hand hygiene
- Nutrition
- Sedation, analgesia and neuromuscular blockade
- Thromboprophylaxis
- Stress ulcer prophylaxis
- Weaning from mechanical ventilation
- Sugar control
- Traumatic brain injury
- Abdominal compartment syndrome
- Catheter-associated urinary tract infection (CAUTI)
- Myocardial infarction
- Intensive care unit (ICU) design
- Red blood transfusion
- Corticosteroid insufficiency
- Brain death and organ donation
- Spinal cord injury
- New onset fever
- Hemodynamic support.

Why these Guidelines and Protocols are Needed

There has been a widespread move toward developing clinical practice guidelines, which are designed to improve the quality of healthcare, to reduce the use of unnecessary, ineffective or harmful interventions and to facilitate the treatment of patients with maximum chance of benefit, with minimum risk of harm, and at an acceptable cost.

Recent research has shown that clinical practice guidelines can be effective in bringing about change and improving health outcomes. But they are just one element of good medical decision making, which also takes account of patients' preferences and values, clinicians' values and experience, and the availability of resources.

Traditionally, guidelines have been based on the development of consensus among experts, although this process has limitations and can lead to flawed conclusions. There is now growing recognition that guidelines should be based, where possible, on the systematic identification and synthesis of the best available scientific evidence. Clinical practice guidelines will be effective only if they are perceived to be helpful and are actually used in clinical decision making.

Potential Benefits of Clinical Practice Guidelines

Potential Benefits for Patients

- To improve health outcomes.
- To promote interventions of proved benefit and discourage ineffective ones have the potential to reduce morbidity and mortality and improve quality of life, at least for some conditions.
- To improve the consistency of care.
- Cost-effective.
- To provide material of information of general public through media.
- *To help in decision making*: Increasingly, lay guidelines summarize the benefits and harms of available options, along with estimates of the probability or magnitude of potential outcomes.
- Call attention to under recognized health problems, clinical services, and preventive interventions and to neglected patient populations and high-risk groups.

Potential Benefits for Healthcare Professionals

- To improve the quality of clinical decisions. They offer explicit recommendations for clinicians, who are uncertain about how to proceed, overturn the beliefs of doctors accustomed to outdated practices, improve the consistency of care, and provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies.
- Guidelines based on a critical appraisal of scientific evidence (evidence-based guidelines) clarify which interventions are of proved benefit and document the quality of the supporting data. They alert clinicians to interventions unsupported by good science, reinforce the importance and methods of critical appraisal, and call attention to ineffective, dangerous and wasteful practices.
- To support quality improvement activities.
- Guidelines are a common point of reference for prospective and retrospective audits of clinicians' or hospitals' practices: the tests, treatments and treatment

by mansdocs.com

goals recommended in guidelines provide ready process measures (review criteria) for rating compliance with best care practices.
- Medical researchers benefit from the spotlight that evidence-based guidelines shine on gaps in the evidence.
- Choice of experts.
- Makes record amenable to audit.
- Eradicates omissions.
- Reduces confusion of staff.
- Makes use of resources optimally.
- Brings uniformity to patient management.

Potential Benefits for Healthcare Services

- Healthcare systems that provide services, and government bodies and private insurers that pay for them, have found that clinical guidelines may be effective in improving efficiency (often by standardizing care) and optimizing value for money.
- Reduces outlays for hospitalization, prescription drugs, surgery and other procedures.
- Improve public image, sending messages of commitment to excellence and quality.

Potential Limitations and Harms of Guidelines

- The most important limitation of guidelines is that the recommendations may be wrong (or at least wrong for individual patients).
- Scientific evidence about what to recommend is often lacking, misleading or misinterpreted. Recommendations are influenced by the opinions and clinical experience and composition of the guideline development group.
- Patients' needs may not be the only priority in making recommendations. Practices that are suboptimal from the patient's perspective may be recommended to help control costs, serve societal needs or protect special interests (for example, those of doctors, risk managers or politicians).

Potential Harms to Patients

- Recommendations that do not take due account of the evidence can result in suboptimal, ineffective or harmful practices.
- Guidelines that are inflexible can harm by leaving insufficient room for clinicians to tailor care to patients' personal circumstances and medical history. What is best for patients overall, as recommended in guidelines, may be inappropriate for individuals; blanket recommendations, rather than a menu of options or recommendations for shared decision making, ignore patients' preferences. Thus, the frequently touted benefit of clinical guidelines—more consistent practice patterns and reduced variation—may come at the expense of reducing individualized care for patients with special needs.
- Lay versions of guidelines, if improperly constructed and worded, may mislead or confuse patients and disrupt the doctor-patient relationship.
- Recommendations against an intervention may lead providers to drop access to or coverage for services. Imprudent recommendations for costly interventions may displace limited resources that are needed for other services of greater value to patients.
- The tendency of guidelines to focus attention on specific health issues is subject to misuse by proponents and advocacy groups, giving the public (and health professionals) the wrong impression about the relative importance of diseases and the effectiveness of interventions.

Potential Harms to Healthcare Professionals

- Flawed clinical guidelines harm practitioners by providing inaccurate scientific information and clinical advice, thereby compromising the quality of care.
- They may encourage ineffective, harmful or wasteful interventions.
- Even when guidelines are correct, clinicians often find them inconvenient and time consuming to use.
- Conflicting guidelines from different professional bodies can also confuse and frustrate practitioners.
- Outdated recommendations may perpetuate outmoded practices and technologies.
- Auditors and managers may unfairly judge the quality of care based on criteria from invalid guidelines.
- The well-intentioned effort to make guidelines explicit and practical encourages the injudicious use of certain words (for example, "should" instead of "may"), arbitrary numbers (such as months of treatment, intervals between screening tests) and simplistic algorithms when supporting evidence may be lacking.
- Algorithms that reduce patient care into a sequence of binary (yes/no) decisions often do injustice to the complexity of medicine and the parallel and iterative thought processes inherent in clinical judgment.

by mansdocs.com

- Guidelines are also potentially harmful to doctors as citable evidence for malpractice litigation and because of their economic implications.
- A negative (or neutral) recommendation may prompt providers to withdraw availability or coverage.
- A theoretical concern is that clinicians may be sued for not adhering to guidelines although, as discussed in the third paper in this series, this has not yet become an important reality.
- Guidelines can harm medical investigators and scientific progress if further research is inappropriately discouraged.
- Guidelines that conclude that a procedure or treatment lacks evidence of benefit may be misinterpreted by funding bodies as grounds for not investing in further research and for not supporting efforts to refine previously ineffective technologies.
- Guidelines cover 60–90% of relevant cases.
- Last but not the least, most of the Critical Care Guidelines have not included Indian patients, so extrapolating their results in our settings may not be reliable.

Potential Harms to Healthcare Systems

- Healthcare systems and payers may be harmed by guidelines if following them escalates utilization, compromises operating efficiency or wastes limited resources.
- Some clinical guidelines, especially those developed by medical and other groups unconcerned about financing, may advocate costly interventions that are unaffordable or that cut into resources needed for more effective services.

CONCLUSION

Standard guidelines are needed to increase ethical awareness, improve trial methods, to prevent frauds and accidents during trials, mutual recognition of data, have safe clinical practice and appropriately use research and development funds. Good clinical guidelines should be valid (leading to the results expected of them), reproducible (if using the same evidence, other guidelines groups would come to the same results), cost-effective (reducing the inappropriate use of resources), representative/multidisciplinary (by involving key groups and their interests), clinically applicable (patient populations affected should be unambiguously defined), flexible (by identifying the expectations relating to recommendations as well as patient preferences), clear (unambiguous language, which is readily understood by clinicians and patients, should be used), reviewable (the date and process of review should be stated) and amenable to clinical audit (the guidelines should be capable of translation into explicit audit criteria). Finally, the guideline is the guide for which path you choose, but the selection depends on patient, skill, budget and experience of individual. Ultimately clinical guidelines are only one option for improving the quality of care.

BIBLIOGRAPHY

1. Eddy DM. Clinical decision making: from theory to practice. Designing a practice policy. Standards, guidelines, and options. JAMA. 1990;263(22):3077, 3081, 3084.
2. Effective healthcare. Bulletin No. 8. Implementing Clinical Guidelines. Leeds: University of Leeds; 1994.
3. Eichacker PQ, Natanson C. Evaluating guidelines for critical care: a need for detail. Intensive Care Med. 2010; 36:1631-2.
4. Feder G, Eccles M, Grol R, et al. Clinical guidelines: using clinical guidelines. BMJ. 1999:318:728-30.
5. Lenfant C. Shattuck lecture—clinical research to clinical practice—lost in translation? N Engl J Med. 2003;349(9): 868-74.
6. Liberati A, Pistotti V, Telaro E. Evidence-based medicine and practice: what's new for physicians? Forum (Genova). 1999;9(4):361-71.
7. NHS Executive. Clinical guidelines. Leeds: NHSE; 1996.
8. Rebecca Broughton. What makes a good clinical guideline? Hayward Medical Communications, www.evidence-based-medicine.co.uk. Vol. 1, No. 11; 2001.
9. Roche N, Durieux P. Clinical practice guidelines: from methodological to practical issues. Intensive Care Med. 1994;20: 593-601.
10. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomed Imaging Interv J. 2008;4(1):e5.
11. Woolf SH, Grol R, Hutchinson A, et al. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ. 1999;318(7182):527-30.

by mansdocs.com

CHAPTER

13

Clinical Audit and Handoff in ICU

Mohammad Omar Faruq

CLINICAL AUDIT IN ICU

The issue of appropriately defining and measuring the quality of healthcare is central to improving clinical practice. One potentially powerful and widely used method of quality improvement is to establish the extent to which clinical practice complies with identified numerous criteria. The degree of compliance or lack of it highlights areas where improvements can be made. This is the basis of clinical audit.

Clinical audit is a process that has been defined as a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit condition and the implementation of change.

Historically, one of the first ever clinical audits was undertaken by Florence Nightingale during Crimean War in 1853. Nightingale kept meticulous record of mortality of soldiers when she applied strict sanitary routines and standards of hygiene to the field hospital and equipments. Mortality rates fell from 40% to 2%. Her methodological approach as well as the emphasis on uniformity and comparability of results of healthcare is still recognized as the earliest programs of outcome management.

Clinical audits are normally carried out by a group of peers working in the same healthcare service or organization. Audit and its feedback are important reinforcement strategies that can help maintain clinician adherence to guidelines. The intensive care unit (ICU) literature suggests that audit and feedback are effective in increasing clinician adherence to guidelines in ICU.

There can be three different types of audits in ICU:

Standard-Based Audit

An audit, which involves defining standards, collecting data to measure current practice against those standards and implementing any changes deemed necessary.

For example, an audit can be undertaken to assess the hand hygiene practices among ICU staff, and their compliance to the expected standard of hand hygiene practice.

Significant Event Audit

This is one of the methods used to peer review cases, which have caused concern or from which there was an unexpected outcome. The multidisciplinary team in ICU discusses individual cases to reflect upon the way the ICU team functioned and to learn from the mistakes or mismanagement (act of commission/act of omission).

Peer Review Audit

An assessment of quality of care provided by the ICU team with a view to improve clinical care. Individual cases are discussed by peers to determine, whether the best care was given. This is similar to significant event audit, but might include interesting or unusual cases. This method is not structured like standard-based audit. There is no systematic method to follow the recommendation made from these reviews.

Clinical audit is an essential pillar of clinical governance. Education and training, risk management, research and development, clinical effectiveness, etc. are

by mansdocs.com

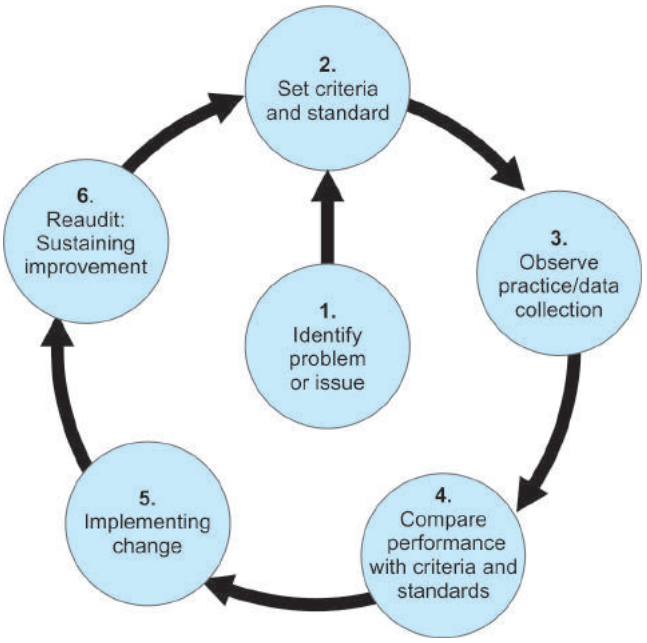


Fig. 1: Audit Cycle.

other important pillars of clinical governance. Like in other clinical settings, clinical audit in ICU can be described as a cycle (Fig. 1). Within the cycle, there are stages that follow the systematic process of establishing the best practice, measuring against criteria, taking action to improve patient care and monitoring to sustain improvement. As the process continues, each stage aspires to a higher level of quality.

Stage I: Identify the Problem or Issue

This stage involves selecting a topic or issue to be audited and is likely to involve measuring adherence to healthcare processes that have been shown to produce best outcomes for patients.

Stage 2: Define Criteria and Standard

Decisions regarding the overall purpose of the audit should be written as a series of tasks that the audit will focus on. These include what should happen as a result of the audit or what questions the audit is meant to answer. Collectively, these form the audit criteria. These criteria are explicit statements that define what is being measured and represent elements of care that can be measured objectively. The standards define the aspect of care to be measured and should always be based on the best available evidence.

Stage 3: Data Collection

To ensure that data collection is precise and that only essential information is collected. Certain details of what is to be audited must be described at the onset and they include type of patient population of ICU, type of health caregivers involved in patient care (i.e. doctors, nurses or both) and the period of audit.

Data may be collected manually using data sheet or electronically using data capture solutions. Considerations are given to what data will be collected, where data will be found and who will do the data collection. Ethical issues must be considered. The data collected must be related to the objective of the audit. Staff and patient confidentiality must be respected.

Stage 4: Compare Performance with Criteria and Standards

This is the analysis stage, whereby the results of the data collection are compared with criteria and standards. The end stage of analysis concludes how well the standards were met and identifying reasons why the standards were not met in all the cases. These reasons might be added to the exception criteria for the standard in future or will suggest a focus for improvement measures.

In practice where standard results were close to 100% of cases, it might be agreed that any further improvement will be difficult to obtain and that other standards with results further away from 100% are the priority targets for action. Only in "life and death" circumstances, it will be important to achieve 100% standard.

Stage 5: Implementation Stage

Once the results of the audit has been published and described, an agreement must be reached about the recommendation for change. Using an action plan to record these recommendations is a good practice. This should include who has agreed to do what, and during what time frame. Each point needs to be well-defined with a designated individual who will be responsible for it and has agreed to a target for completion.

Stage 6: Reaudit: Sustaining Improvements

After an agreed period, the audit should be repeated. The same strategies for identifying the sample, methods and data analysis should be used to ensure comparability with original audit. The reaudit should demonstrate that the changes have been made.

by mansdocs.com

This stage is critical to the successful outcome of an audit process as it verifies whether the changes implemented have had an effect and to see if further improvements are required to achieve the standards of healthcare delivery identified in stage 2.

While clinical audit makes great sense, ICU clinicians often are reluctant to undertake and apply clinical audit in their work. This is partly because clinical audit program often does not result in desired improvements in patient care. There may be several reasons behind this outcome. First, there is often confusion about the differences between clinical audit, service evaluation and research. Some audit projects may cross the fine line between audit and research, not actually assessing performance against accepted standards, but continually redefining those standards. Secondly, while in theory clinical audit takes the form of a neat cycle (described earlier) of identifying problem, defining standards, collecting data, implementing change and reauditing, in the real world of clinical medicine, the cycle is often not completed and the problem is not resolved. One United Kingdom study identified that audit cycle was completed in 25% of cases.

As clinical audit lead, chief of ICU has a clear role in creating strategy for embedding clinical audit within the unit. He must campaign clinical audit among both to his colleagues and hospital management alike. The clinical audit lead should be actively involved with other aspects of clinical governance in ICU to allow for the dissemination of clinical audit information and the setting of clinical audit priorities in ICU.

HANDOFF IN ICU

"Handoff" of patient care communication is a real-time interactive process of passing patient specific information from one caregiver to another for the purpose of ensuring the continuity and safety of patient's care. The working definition for a patient handoff is "The process of transferring primary authority and responsibility for providing clinical care to a patient from one departing caregiver to one oncoming caregiver". Caregivers include consultants/attending physicians, resident physicians, physician assistants, registered nurses, etc.

The requirement of the Joint Commission of USA (formerly known as Joint Commission on Accreditation of Healthcare Organizations) to implement a standardized approach to "handoff" communications and transition in healthcare has opened doors of opportunity to improve healthcare quality and safety. This information transfer problem has always plagued patient care in ICU similar to other services of healthcare organizations.

When critical information is not transferred between caregivers, effective communication breaks down placing patient at risk for errors or omissions in care.

Communication errors are reported as root cause in the majority of sentinel events in healthcare. The Joint Commission identified communication as the top contributing factor of medical errors (65% of sentinel events reported were caused by communication problem). In 2005, that percentage rose to 70% with an analysis identifying "at least half of the communication breakdown occurring during handoffs".

This information coupled with studies revealing that a majority of adverse events are due to the lack of effective communication (i.e. lost information, misinterpretation, misdirected or missed actions), which has spurred a movement to improve communication within and between healthcare teams.

Concise and goal directed patient handoff is perhaps the most important in emergency situation where even a small delay in diagnosis and treatment could lead to significant morbidity and mortality. A delay in initiation of assisted ventilation in the ICU setting less than a minute to more than 3 minutes correlated with a decrease in favorable outcome from 21% to 0% in one study. Initiation of cardiopulmonary resuscitation within 3 minutes of cardiac arrest was associated with a 25% increase in survival compared with delayed support in another study.

The handoff communication is the verbal and or written exchange of patient information occurring during transfer of responsibility and care giving activities. Briefings or huddles are similar to handoffs, and suggest a method of bringing together like practitioner or team to obtain a clear picture of the current status before or after a transient absence (relief for lunch or a break) and during momentary cross covering, while one professional is focused on another task or at the beginning of a procedure or event. Handoff has received many different names: sign out, shift report, handover, checkout, sign over, etc. creating a sense of ambiguity on what precisely constitutes a handoff.

According to the Joint Commission, which requires that, hospitals implement a standardized approach to handoff communication including an opportunity to ask and respond to questions. The primary objective of handoff is to provide accurate information about a patient's care, treatment and services, current conditions and any recent or anticipated changes.

by mansdocs.com

The information communicated during handoff must be accurate to meet the patient safety goals. Hence, accuracy of a handoff hinges on the effectiveness of the communication between two or more individuals. Unfortunately, high reliance on communication is prone to human errors such that incomplete or poor quality handoffs have been implicated as a source of adverse events or near misses in hospitalized patients. Furthermore, increase in number of shifts in units like ICU (e.g. 12 hourly shifts in place of 24 hourly shifts) has produced increase in number of handoffs and has led to a reduction in continuity of patient care. Each time a patient is handed over to another healthcare provider, the risk of developing an adverse event increases.

High quality care takes into consideration patient's condition, current status and prior treatment and applies them to decision making, patient management and efficient handoffs when responsibility for patients are transferred. Research has identified the handoff as a vulnerable period in the care process during which information may be lost, disrupted or misinterpreted.

Recent literatures suggest that ineffective handoff can lead to the following negative consequences which are commonly observed in ICU:

- Wrong treatment
- Delay in medical diagnosis
- Life threatening adverse events
- Patient complaints
- Increased healthcare expenditure
- Increased hospital length of stay
- Litigation.

It is customarily asked in ICU, "what kind of information should be included in handoff?" Handoff should give the accepting clinicians a snap shot of patient information that will enable immediate provision of seamless care. Handoff is not a comprehensive communication of every detail of patient's history or clinical course. Too much data may mask or bury important information that the next provider needs. For example, instead of listing all medications, new medications are discussed that requires monitoring and adjustment and suggestions for medication that should be ordered if certain clinical events occur. Planned clinical test results with planned diagnostic procedures are communicated with the plan of care associated with the results. It should be noted that requirement of a standardized handoff is primarily verbal. However, it is better to have a written component in addition that could relate to notes, personal digital assistant (PDA) or computer entries.

The following are the standard elements that required in an ideal handoff communication in ICU. The mnemonic IDEAL is described below:

Identify—Patient's name, medical record number, date of birth and physician's name.

Diagnosis—Diagnosis and current condition.

Events—Recent events/changes in condition or treatment.

Anticipated—Anticipated changes in condition or treatment, what to watch for in next interval of care and contingency plans.

Leave—Leave time for the opportunity to ask questions and clarify information.

There are four different types of handoff communication practiced in ICU depending on the location of services and provider types.

1. *Change in level of care*:
   - From ICU to intermediate care unit or general ward
   - From emergency department to ICU.
2. *Temporary transfer of care*:
   - From ICU to operating room, hemodialysis unit, procedure area, bronchoscopy suite, etc.
3. *Discharge*:
   - Communication to next care provider in a nursing home or another hospital in case of direct discharge from ICU.
4. *Change in provider or change in services*:
   - Resident or medical officer sign out
   - Nurse change of shift
   - Rotation change (new batch of house staff or faculty replacing the old ones).

The change in the provider involves the most clinically important type of handoff communication in ICU. The resident or medical officer handoff during change of provider, at the end of the shift, requires the following methods for a successful handoff communication.

- Face-to-face verbal updates with interactive questioning
- Limit any interruption during update
- Use additional updated information for team mates (other than one being replaced)
- Outgoing read back to ensure that information was accurately received
- Include outgoing team's opinion toward on coming's changes to plan and contingency plans
- Outgoing writes summary before handoff
- Oncoming assess current status
- Oncoming scans historical data
- Oncoming reviews data changes informed by outgoing

by mansdocs.com

- Use clear language. Avoid using confusing statements like she is "a little unstable", "somewhat lethargic", "exaggerating her pain", etc.

The intensive care unit team may use standard tools that can facilitate consistency in communication exchanges. In the literature, there are several mnemonics that can be used as tool to guide standard handoff and optimize information transfers. These are useful supplements to verbal communication and can facilitate consistency in communication exchanges. Two popular mnemonics, *I SBAR* (stands for Introduction, Situation, Background, Assessment and Recommendation) and I *PASS* the *BATON* are worth mentioning. The latter is found to be useful and comprehensive and is described below.

I (Introduction)—Introduce yourself and your role/job

P (Patient)—Name, identifier, age, sex, location

A (Assessment)—Presenting chief complaints, vital signs, symptoms and diagnosis

S (Situation)—Current status, medication, code systems, response to treatment

S (Safety concerns)—Critical laboratory values, allergies

The

B (Background)—Comorbidities, previous episodes

A (Actions)—What actions were taken or required

T (Timing)—Level of urgency, prioritization of action

O (Ownership)—Who is responsible (doctors/nurse/team)

N (Next)—Anticipated changes, contingency plans.

In spite of using these "tools" which help to make ICU handoff more convenient, clinicians often face the following barriers against effective handoff communication in ICU.

- Handoffs are often truncated or omitted due to work demands or time constraints resulting from duty hour limits with documentation replacing all or some of the interactive exchange.
- Diagnostic and care activities unfinished at the end of the outgoing shift and carried through a shift change which put them at higher risk of being dropped.
- Handoff participants perceived as not trusting each other with lack of confidence in the outgoing or not knowing each other.
- Handoff under cross coverage due to large patient loads, low familiarity with patients and an expectation of less information needing.
- Coordination problem and lack of sense; which resident of the team is responsible for which patient.

Bedside handoff is an integral part of a standardized handoff process in ICU. Time constraint often affects the bedside handoff process when the handoff process is followed by ICU round involving consultant/attending physicians and the ICU team at a designated rigid time frame. There are three different strategies which shape ICU bedside handoff before the round begins with the consultant.

Strategy I (Also Called Bed to Bed, Make Sure all is Said)

The presumed form of a handoff is geographic strategy in which the clinician begin their patient discussion at first bed in ICU. They then proceed across the unit in precise order moving from bed to bed in methodic manner. Each patient is discussed in turn, as the clinicians stand at bedside of the patient. They can see the next patient and anticipate what to follow by knowing what has been completed and what lies ahead. The handoff pace can be altered as needed. The key feature of this geographic handoff is a soft time constraint. Most handoff in ICU belongs to this category.

Strategy II (Also Called Save the Sick, Do the Others Quick)

This particular handoff has a rigid time constraint of which the on comings and out goings are aware before the handoff begins. The sign out needs to be completed before the consultant round begins. For example, the shift changes at 7.30 AM and the consultant round begins at 8 AM. So the sickest, most unstable and critical patient gets the most attention during this half hour and the stable patients are quickly presented and handed off.

Strategy III (Also Called New Demand, Change the Plan)

In this strategy, the clinicians (oncoming and outgoings) begin with a geographical strategy. They proceed from bed to bed until they reach the bed five who is the most critical patient. An obstacle arises at this point as another patient goes into cardiac arrest. As a result handoff is truncated or interrupted. One or two residents from the incoming or outgoing group rush to manage the cardiac arrest. However, the handoff continues at bed five as everybody is aware that critical information must be submitted concisely and urgently. So handoff continues at bed five until the designated time is over. The remaining seconds are spent on concise statements about few other patients with one or two sign out details.

by mansdocs.com

It has been observed that ICU residents and medical officers are not formally educated in sign out skills and are not given this knowledge through informed mechanisms. Feedback is usually not provided to them regarding the quality and contents of their sign outs. The following steps are known to improve quality and outcome of residents' handoffs.

- First, teaching residents how to do handoff early in their training is essential. It should focus equally on clinical decision making and communicating the information clearly and effectively.
- Second, the use of cross coverage should be examined and where possible eliminated. In cross-coverage situation, resident outside ICU often covers ICU patients, and in other situation, resident of ICU covers patients out of his unit. So there is an increased odd for errors and surprises.
- Third, increased involvement by senior residents and faculty could create an environment for individuals to learn the ins and outs of the communications and techniques of handoff.

In conclusion, patient care quality and safety in ICU can be improved during handoffs when physicians, nurses and clinical champions join leadership in making handoffs a system priority. Handoffs need to be redesigned based on best practices and human functions research using successful communication techniques and strategies. ICU in charge should play a leadership role in initiating improvement in hands-off program within his unit, setting the priority and identifying the timeline.

BIBLIOGRAPHY

1. Anderson P, Fee P, Shulman R, et al. Audit of audit: review of a clinical audit programme in a teaching hospital intensive care unit. Br J Hosp Med (Lond). 2012;73(9):526-9.
2. Australian Council for Safety and Quality in Healthcare. Clinical Handover and Patient Safety: Literature review report. 2005. 1-31.
3. Gandhi TK. Fumbled handoffs: one dropped ball after another. Ann Intern Med. 2005;142(5):352-8.
4. National Institute of Clinical Excellence. Principles of best practice in clinical auditing. London: NICE; 2012.
5. The Joint Commission Improving handoff communications. Improving hand off communications: meeting national patient safety goal 2E. Joint Perspective on Patient Safety. 2006;6(8):9-15.

by mansdocs.com

CHAPTER

14

Critical Care Nursing in India

Arindam Kar, Sati Chakrabarti, V Ruth Adora Rao, Manish Munjal, Neena Rungta, Narendra Rungta

INTRODUCTION

In the face of being the seventh largest country by area, second most populous with over 1.2 billion people, India has become one of the fastest growing economies and continues to face serious challenges like poverty, terrorism, malnutrition, poor literacy and inadequate public healthcare.

The World Bank cautions that to achieve its economic potential India must concentrate on public sector reform, transport infrastructure, agricultural and rural development, removal of labor regulations, education, energy security, and public health and nutrition.

Speaking of public health, India has a universal healthcare delivery system which is governed by the states and territories. The citizens are entitled to free basic and primary healthcare and people who afford better care turn to private care facilities for a cost. Quality of healthcare varies across the cities and villages, government and private care facilities.

The healthcare system is interdisciplinary and comprises of professionals like physicians, nurses, dieticians, physiotherapists so on and so forth. Healthcare is essentially teamwork and it goes without saying that any team is as strong as its weakest link.

It is every professional's moral obligation to work toward the development of his or her profession.

In Rawasi Williams's words "To do what nobody else will do, in a way that nobody else can do, in spite of all we go through; is to be a nurse".

Nursing as a discipline can be traced back to times immemorial, where women of the household tended to the sick and injured in the family. It all started and gained recognition as a profession when Florence Nightingale cared for the war wounded in the Crimean War in 1853. She observed the fact that most of the soldiers were dying because of acquired infections, poor hygiene, supplies and nutrition. She used and propagated hand hygiene measures, cohorted the sick patients and recognized the need of increased frequency of monitoring the sicker patients. This was, infact the first such attempt to organize a temporary intensive care unit and practice hand hygiene, which form the basis of modern critical care medicine today.

Nursing, as a profession has come a long way since the Crimean War times. Today, it is an established discipline with its own sub specialties like medical surgical, geriatric, pediatric, obstetric, cardiovascular, oncology and neurology nursing.

According to Trained Nurses Association of India (TNAI) in India, the nurse to doctor ratio is almost 1.5:1, while it is 3:1 in developed countries. In the interest of patient care, the National Health Policy (NHP) emphasizes the need for an improvement in the ratio of nurses vis-à-vis doctors or beds. It also emphasizes on improving the skill level of nurses and increasing the ratio of nurses with a bachelor's degree in nursing as compared to those with diploma in nursing. It further recognizes the need for establishing training courses for super-speciality nurses required for tertiary care institutions. The WHO estimates a shortage of

by mansdocs.com

Table 1: Institutions offering various programs and the total capacity.

S. No	Program	Number of institutions		Total	Capacity
1.	ANM	Government	310	1,489	39,325
		Private	1,179		
2.	GNM	Government	199	2,550	101,620
		Private	2,351		
3.	B.Sc (N)	Government	83	1,516	75,748
		Private	1,433		
4.	M.Sc (N)	Government	30	483	9,200
		Private	453		

Source: http://www.tnaionline.org/bifeb-13/7.htm
(ANM: Auxiliary nursing and midwife; GNM: Graduate non-matriculated).

more than 4.5 million doctors, nurses, midwives and others. To improve this condition, strong political commitment is required on the part of government. The following is the picture of the number of private and government institutions offering various programs and the total capacity. Various surveys show that the demand of nurses far exceeds the number of new nurses being inducted into the system (Table 1).

The number of nurses coming out of nursing schools is quite small compared to the country's need, leaving a big gap between supply and demand of nurses.

Nursing care is administered in various settings, acute or emergent care and general care areas. Each care setting has its own requirements of healthcare professionals. Nurses who work in acute care areas deal with critically ill patients who require single or multiple organ support and intensive monitoring. The nurses working in intensive care units should have qualification and training in critical care, which is largely unavailable in India.

As India's economy and healthcare infrastructure is growing at a rapid pace, it is necessary that we have a large pool of professional nurses to meet the requirement. This may require opening more nursing schools, better training and job opportunities for the nurses.

The public opinion of a critical care nurse in India is that of a professional who provides basic care like feeding, cleaning, administering medicines as prescribed. She is considered subordinate to the physician with little contribution to the planning and execution of treatment in a critically ill patient. One of the main reasons is the disparity in education amongst the nurses due to variations in entry criteria as well as teaching and training standards. Presently, in India there are six levels of nursing education with different qualification required for entry into the courses.

QUALITY OF EDUCATION

The quality of nursing education in India is regulated by the Indian Nursing Council (INC)—a statutory body that regulates nursing education in the country through prescription, inspection, examination, certification and maintaining its stands for a uniform syllabus at each level of nursing education. In an effort to improve quality of education, the INC has increased the duration of graduate nonmatriculated (GNM) program from 3 years to 3.5 years. This increase in the period of internship of student nurses would enhance their exposure to direct patient care and management. The INC should regulate nursing education across the country stringently to bring uniformity in nurses training, upgrading the standards of training schools and create a large pool of qualified nursing teachers. The quota for seats in colleges and schools of nursing has been raised by the INC and complementing this move is the stringent rule and regulation laid down by the INC, all this promises both good quality and quantity of nurses.

Bedsides, clinical nursing is considered very demanding and many qualified nurses prefer teaching assignments which are day assignments, with weekly holidays and are less demanding.

The INC also offers M.Phil and Ph.D programs for nurses under the tutelage of guides approved by INC.

Distance Education

Nurses who are already in working and cannot afford to leave job to attend regular school or college can avail the facility of distance learning and numerous online courses.

Foreign Exchange Program

A number of organizations abroad are encouraging student exchange programs which expose the Indian nurses to culturally diverse population and different care setting. The care facilities and training programs in the west are more advanced. They offer exposure to high quality care, modern technology and are very useful. (For detail, visit the web site: http://www.nursing-midwifery.uq.edu.au/student-exchange)

HUMAN RESOURCES AND NURSING

Human resources (HR) in a hospital plays an important role in strengthening the nursing management which translates into better healthcare delivery. HR manages the nursing workforce and carefully negotiates the demands

by mansdocs.com

of the nurses with the management. It facilitates continuing nursing education (CNE) programs, better working conditions and competitive salaries.

Nurses have a unique potential to influence healthcare delivery system in India. Improvements in the standards of nursing will improve the healthcare delivery in India.

Nursing recruitment is an important issue. There is shortage of trained nurses and many private hospitals or hospital chains enter into a tie-up with nursing schools besides doing campus recruitment. These freshers are assigned a preceptor (senior nurse) in the hospital, who supervises their training and grooms them for the respective nursing assignments.

Quality of education, internship and on job training is a huge intervention that affects the quality of care.

Employer and employee relation: Employer and employee relation is another issue where the administrators and employers consider nurses to be submissive and reluctant to voice their concerns and issues.

Poor reimbursement: Poor reimbursement is a major deterrent for the younger generation to choose nursing as a profession in India. Hospitals do not charge for the nursing services unlike many other services like dietetics, physiotherapy. The nursing charges are included in the ICU bed charges. Although the cost of ICU care is increasing every year, it is not translating into better salary for the nurses. Other deterrents include lack of adequate insurance, post retirement benefits, study leave and maternity benefits.

Work conditions: Most Indian ICUs do not have dedicated 1:1 nurse-patient ratio even for the critically ill patients. Generally accepted norm is 1:2 nurse-patient ratio, which may deteriorate in case the occupancy is high or there is overcrowding in the ICU. This demoralized the overworked nurses as they are unable to deliver quality care to their patients and leave them dissatisfied.

Occupational hazards: Nurses working in healthcare facility are constantly at risk of hazards like harmful radiation, airborne and contact transmitted pathogens. Long-standing hours predispose them to backache, stress and development of varicose veins. The time-outs are limited to tea, lunch and dinner breaks only with hardly any recreational activity during working hours.

Nurse-patient ratio: This differs across the length and breadth of the nation. Accredited hospitals ensures adequate nurse-patient ratio (1:1 in acute care setting and 1:2–3 in step-down units) but the same is not the situation in many other hospitals. This inadequacy in nurse-patient ratio leads to increased scope for errors, inadequate patient care, unhappy patients, increased costs, increased length of hospital stay and morbidity besides nurses' job dissatisfaction.

Changing trends in healthcare: Changing trends in health care in terms of early discharges to reduce length of ICU and make it cost effective. The patients are being discharged early and a new class of home support workers that include nurses, untrained and unqualified staff provide home care to these patients. This results in faster readmissions, increased morbidity and overall high cost. Home care delivery by unqualified staff may invite consumer and legal issues.

Aging nurses' population: Studies have shown that a larger part of the nursing population is aging and we need more youngsters to take up nursing as profession and the nurses to collectively raise their voices to uplift themselves by making themselves heard by the right people.

Cultural variation: A large number of nurses come from the state of Kerala in South India. The number of nursing schools in the southern states is very high as compared to rest of India. In the last few years, nursing profession has become quite popular in the northeast and many girls are choosing nursing as a career. However, language and communication emerge as the core issues when go out to work in different states of India.

The speciality of critical care nursing is firmly established in India now and is evolving at a good pace. The Indian Society of Critical Care Medicine (ISCCM) has recognized the importance of nurses trained in intensive care and has started a diploma in critical care nursing 1 year recently.

The Indian Diploma in Critical Care Nursing (IDCCN) offers a comprehensive and structured program under the mentorship of trained intensivists. Presently, the program is available at all Indian Diploma in Critical Care Medicine (IDCCM) centers approved by ISCCM and the seats available for IDCCN are double the IDCCM seats. The centers and the number of seats may increase in near future. Upon successful completion of the 1 year program (theory and practical) the students will be awarded certificates by the Indian College of Critical Care Medicine.

Besides the IDCCN course, the American Association of Critical-Care Nurses offers an online certification which can found at http://www.aacn.org/. The Indira Gandhi Open University offers a 6-month diploma in critical care at the www.ignou.ac.in › School of Health Sciences › Programmes.

by mansdocs.com

The lower payments, poor working conditions and stressful lives are forcing the nurses to look for greener pastures outside India. This has created a significant shortage in the number of nurses available in critical care.

A "Train the Trainer Program" has been initiated by the authors in their hospital, where the nurses selected from the Critical Care Units are trained by the intensivists. These nurses are actively involved in assessing, planning and executing patient care in the acute care areas. These "trained trainers" in turn are actively involved in conducting special continuing nursing education (CNE) for the critical care nurses.

The customized module comprises of 12 modules in sets of three. The first set comprising of basics of critical care nursing is compulsory for everyone opting for the program. Regular attendance and a score of 60% in the theory exam makes the student eligible for the next set of modules. Timely completion of all the 12 modules in 2 years time makes the nurse eligible for an extra 25% raise in the salary. This was an effort on behalf of the authors to lure their nurses into continuing education seeded with the promise of incentives. The authors have also conducted a 2-day comprehensive program designed in collaboration with the ISCCM in places like Guwahati, Shillong, Bhubaneswar, Siliguri, Andamans and in their own hospital in Kolkata last year.

A critical care nurse needs to be abreast of all recent advances in the profession both at the national as well as at the international level. Some useful links related to critical care medicine and nursing are given at the end of the chapter.

You may not always have a comfortable life and you will not always be able to solve all of the world's problems at once but do not ever underestimate the importance you can have because history has shown us that courage can be contagious and hope can take on a life of its own.

Michelle Obama

BIBLIOGRAPHY

1. Biatello LM, Alam H, Allain RM. Critical Care Handbook of the Massachusetts General Hospital. Philadelphia: Lippincott Williams & Wilkins; 2010.
2. Marino PL. ICU Book, 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2007.
3. Udwadia FE. Principles of Critical Care, 2nd edition. India: Oxford University Press; 2005.

IMPORTANT LINKS

- http://www.ccmtutorials.com/
- http://www.crit-nurse.com/index.php
- http://www.isccm.org/education
- http://www.itunes.apple.com/gb/app/oxford-handbook-critical-care/id334679311?mt=8
- http://www.m2hnursing.com/MedCal/module1_1.php
- http://www.sccm.org/Pages/default.aspx
- http://www.uptodate.com/cotents/table-ofcontents/cardiovascular-medicine/critical-caremedicine

by mansdocs.com

SECTION 2

Cardiac Care

by mansdocs.com

by mansdocs.com

CHAPTER

15

Acute Coronary Syndrome

Suresh Ramasubban

DEFINITION

The consensus guidelines by the American Heart Association (AHA) define myocardial infarction (MI) as the presence of myocardial necrosis in a clinical setting due to myocardial ischemia.

From this definition, it is obvious that for a diagnosis of acute coronary syndrome (ACS) any one of the following criteria needs to be met:

- There should be a detectable rise and/or fall of cardiac biomarkers with evidence of myocardial ischemia as demonstrated by symptoms of at least one of the following:
  - Symptoms of ischemia (chest pain, chest discomfort or jaw pain)
  - Electrocardiogram (ECG) changes characteristic of new ischemia [ST-T changes or new left bundle branch block (LBBB)]
  - Presence or development of pathological Q waves in ECG
  - New regional wall motion abnormality on echocardiography or loss of viable myocardium on nuclear imaging.

CLINICAL CLASSIFICATION OF MYOCARDIAL INFARCTION

The AHA consensus document classifies clinically patients into five types (Table 1). In post-coronary artery bypass graft (CABG) related, the rise in cardiac biomarkers has to be at least three times the upper limit of normal and in post-percutaneous coronary intervention (PCI) scenario at least five times above to diagnose MI.

Table 1: American Heart Association classification of myocardial infarction.

Type 1	Primary coronary event
Type 2	Secondary coronary event
Type 3	Sudden cardiac death
Type 4a	Percutaneous coronary intervention related
Type 4b	Stent thrombosis related
Type 5	Coronary artery bypass graft related

Clinically, patients with ACS are classified as having either as ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI) on the basis of ECG. The advantage of using the ECG is that it immediately gives us a working diagnosis and also helps us in planning treatment and provides prognosis.

PATHOPHYSIOLOGY

Spontaneous myocardial infarction is related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. MI can be secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

DIAGNOSIS

History and Examination

Classical chest pain of MI is substernal, crushing and radiating to left shoulder/arm. However, pain may be of

by mansdocs.com

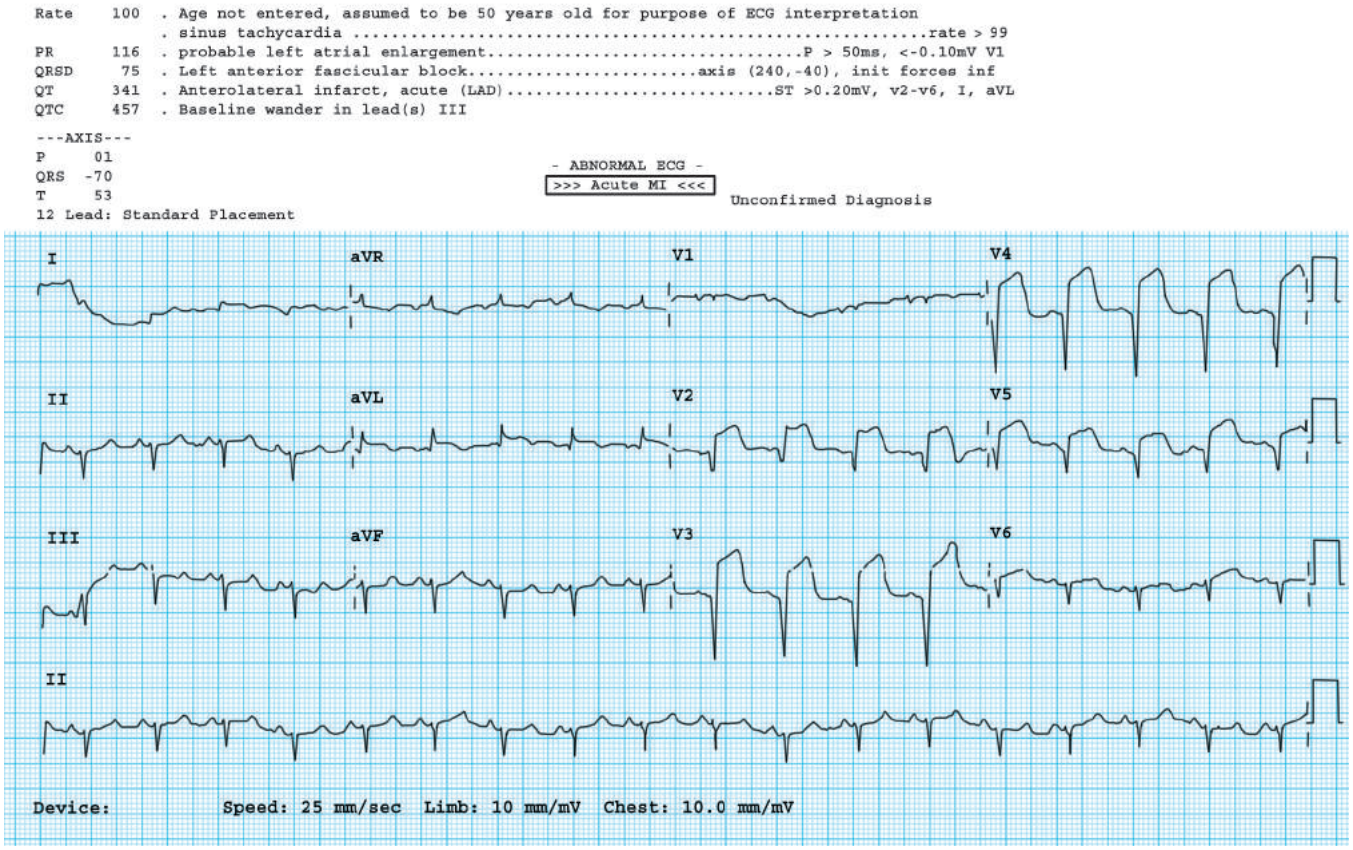


Fig. 1: ST elevation in MI.
(MI: Myocardial infarction).

variable location (jaw, between shoulder blades) and intensity (discomfort, mild pain). Sweating, palpitation, nausea, vomiting, dyspnea or syncope may accompany chest pain. Diabetics and elderly can have a subtle presentation. Examination of a patient with ACS may result in a spectrum of signs ranging from normal to severe hemodynamic collapse manifesting as right or left ventricular failure and even cardiac arrest. Bradycardia is very common (25% of patients) with inferior wall MI. The symptoms and signs may evolve over time so it is important to do repetitive clinical assessment in a patient with ACS, and this is best done in an intensive care unit. The assessment of a patient with chest pain also aims to exclude other life threatening causes of chest pain like aortic dissection, pulmonary embolism, pneumonia, esophageal rupture and cardiac tamponade. The differential diagnosis includes non-life threatening chest pain due to pericarditis, gastroesophageal reflux disease, costochondritis, and anxiety which can be excluded by taking focused history and doing a detailed examination.

Electrocardiogram

An ECG should be obtained immediately while assessing a patient with suspected ACS. If initial ECG is normal or non-diagnostic and suspicion of MI is high, serial ECG's should be obtained. In the absence of LBBB or left ventricular hypertrophy (LVH), the diagnosis of ST elevation can be made following these criteria (Fig. 1).

- ST elevation in two or more contiguous leads (inferior or anterior). Threshold values for ST-segment elevation consistent with STEMI are:
  - J-point elevation 0.2 mV (2 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men more than 40 years old)
  - J-point elevation 0.25 mV (2.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men less than 40 years old)
  - J-point elevation 0.15 mV (1.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (women).

If there is no evidence of STEMI, look for ST depression and T wave changes. A new horizontal or down-sloping ST

by mansdocs.com

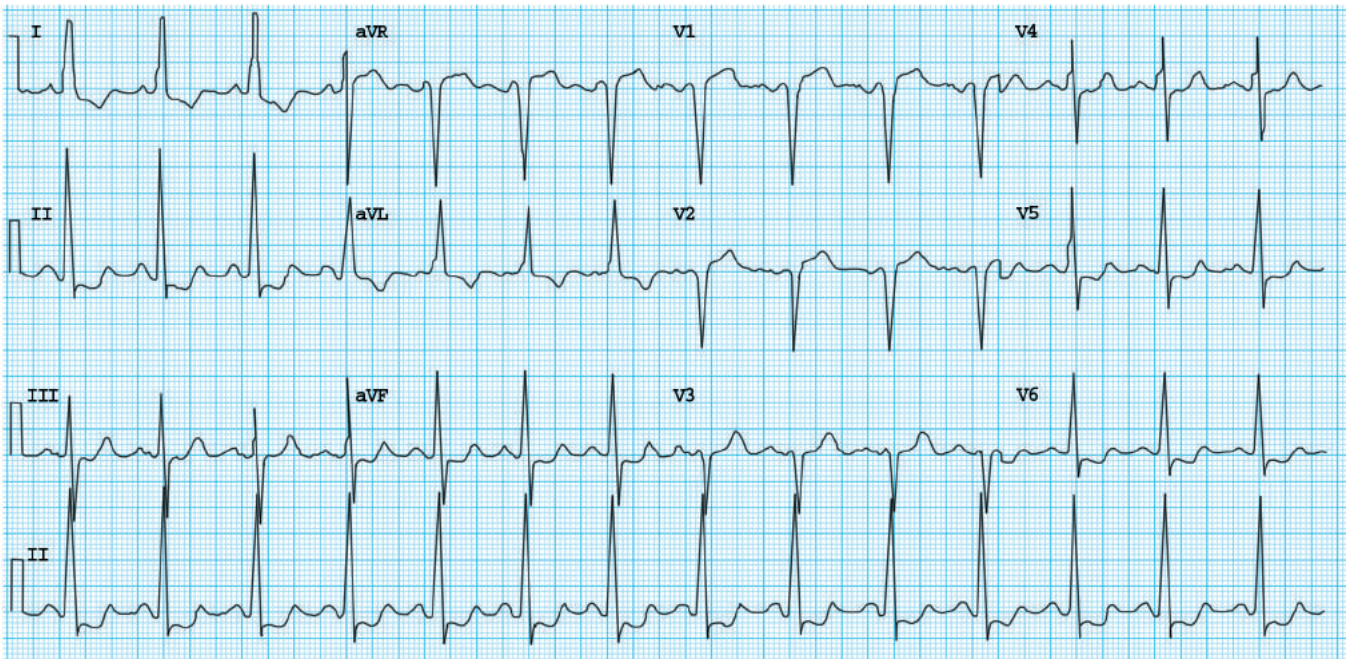


Fig. 2: ST depression in MI.

depression of greater than or equal to 0.05 mV in two contiguous leads and/or T inversion greater than or equal to 0.1 mV in two contiguous leads with prominent R wave or R/S ratio greater than 1 (Fig. 2).

A patient with new LBBB or presumed new LBBB, and symptoms consistent with MI should be treated as STEMI. In the presence of pre-existing LBBB diagnosis of ST elevation is difficult and following criteria can be used:

- ST elevation greater than or equal to 0.1 mV with a positive QRS complex
- ST depression greater than or equal to 0.1 mV in leads V1–V3
- ST elevation greater than or equal to 0.5 mV in leads with a negative QRS complex.

The ECG alone is not enough to diagnose ACS as ST changes may be seen in other conditions such as pericarditis, paced rhythm, LVH, LBBB, Brugada syndrome and in some healthy individuals, and in noncardiac conditions like subarachnoid hemorrhage. ECG alone is non-diagnostic as patients with NSTEMI can have normal ECG.

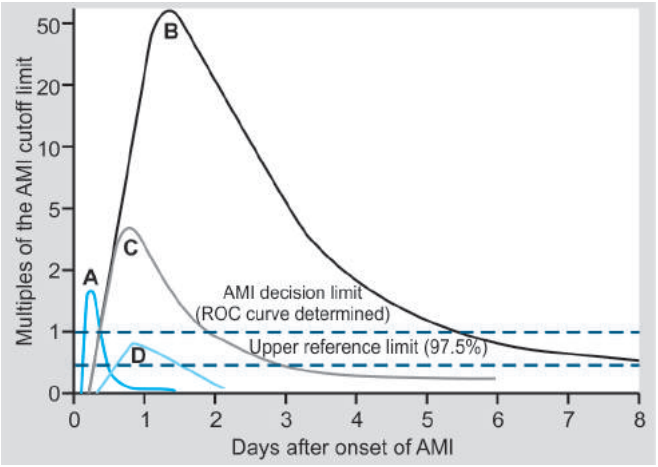


Fig. 3: Cardiac biomarkers in MI.
Peak A: Myoglobin or CK-MB isoforms post-AMI
Peak B: Cardiac troponin post-AMI
Peak C: CK-MB post-AMI
Peak D: Cardiac troponin after unstable angina
(AMI: Acute myocardial infarction; CK-MB: Creatine kinase-MB; ROC: Receiver operating characteristic).

Biomarkers

Troponin

An elevation in biomarkers indicates necrosis of the myocardium. The best biomarker is the troponins (I or T) as it has a sensitivity of 100%, 6 hours after the onset of MI (Fig. 3). Troponin T has a high specificity except in the presence of renal failure and acute skeletal muscle damage wherein troponin I is better. Troponins remain raised for 7–10 days (troponin I) and up to 10–14 days (troponin T).

by mansdocs.com

Creatine Kinase

Creatine kinase (CK) is found in all striated muscles of our body, and the specific isoenzyme CK-MB is the best biomarker when troponins are unsuitable or not available. CK-MB remains elevated only for 3–4 days so a reinfarction in the first 2 weeks can be diagnosed with CK-MB rather than with troponins.

Imaging

Chest X-ray should be a part of routine investigation. Echocardiography is now an important tool available; it is the technique of choice to detect complications of MI. Absence of regional wall motion abnormalities in a patient with chest pain and normal biomarkers has a very high predictive value for ruling out MI.

Laboratory Tests

Routine blood tests like glucose, urea, creatinine, lipid profile, coagulation profile are required for the optimal management of ACS.

RISK STRATIFICATION

Risk stratification in STEMI can be done to predict mortality but, more importantly, it is in NSTEMI that the use of scores like the thrombolysis in myocardial infarction (TIMI) score helps in prognostication as well as management. The TIMI risk score is the simplest to use though the European Heart Association (EHA) has proposed a similar Global Registry of Acute Cardiac Events (GRACE) risk model for predicting death or myocardial infarction following an initial acute coronary syndrome. The TIMI score includes:

- Age greater than 65 years
- Aspirin use in last 7 days
- At least two angina episodes in the last 24 hours
- ST changes of at least 0.5 mm on admission ECG
- Known coronary artery disease
- At least three risk factors for coronary artery disease.

MANAGEMENT

ST-Segment Elevation Myocardial Infarction

Reperfusion

Urgent reperfusion is the treatment of choice in any patient with STEMI. Reperfusion therapy includes primary PCI, fibrinolysis and surgery. The choice of reperfusion therapy is determined by factors like availability of PCI, time to transfer to a facility with PCI and time to presentation. Patients presenting within 3 hours of onset of symptoms, the efficacy of both PCI and fibrinolysis are similar and survival rates are similar. Beyond 3 hours, a meta-analysis has demonstrated superiority of PCI in reducing short-term mortality and reducing rates of reinfarction and stroke. PCI is preferable in the presence of shock and when time to onset of symptoms is not clear or fibrinolysis is contraindicated. Fibrinolysis should be considered in these situations if door to balloon time is greater than 90 minutes for PCI. Fibrinolysis however should be done keeping in mind the absolute and relative contraindications. The fibrin specific agents (alteplase and tenecteplase) are preferred for fibrinolysis in anterior wall MI, if saphenous vein conduit is responsible for MI and patient has had previous exposure to streptokinase. In other situations, streptokinase can be used though revascularization rates may be slightly lower. Surgery (coronary artery bypass grafting) is considered for patients who fail or who have contraindications to both PCI and fibrinolysis, and who meet the criteria of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial. Also surgery is an option for patients with complications like severe mitral regurgitation or free wall rupture. In all other situations, surgery should be postponed till myocardial stunning is resolved.

Anticoagulation

Heparin or low-molecular-weight heparin (LMWH) should be administered to patients following thrombolysis so as to prevent early recurrence of ischemia. LMWH is preferred for at least 48 hours following reperfusion, heparin can be used but with monitoring of activated partial thromboplastin time.

Antiplatelets

All patients with STEMI should receive antiplatelet therapy. A combination of aspirin (160–325 mg orally or chewed) and clopidogrel (300–600 mg orally) should be given as a loading dose. Loading dose of clopidogrel should be avoided in patients above age of 75 years. Subsequently, aspirin (150 mg/day) should be taken indefinitely and clopidogrel (150 mg/day) for 7 days and then 75 mg/day for at least 1 year. Prasugrel (60 mg) can be used as an alternative to clopidogrel. Newest agent is ticagrelor. Dose of ticagrelor is 180 mg stat followed by 90 mg twice

by mansdocs.com

daily. Due precautions should be taken regarding complications such as known allergies and gastric intolerance. Proton pump inhibitors are often used concurrently to prevent gastric complications. These should be spaced out (mainly omeprazole) for 12 hours after clopidogrel to prevent potential drug interaction.

Non-ST-Segment Elevation Myocardial Infarction

The treatment strategy will be on the basis of risk stratification using a score like the TIMI score and certain patient characteristics.

Low-Risk Non-ST-Segment Elevation Myocardial Infarction

In this group of patients close monitoring and use of aspirin alone is sufficient. They should be investigated for inducible ischemia and further therapy planned based on the results of such testing.

High-Risk Non-ST-Segment Elevation Myocardial Infarction

High-risk patients include patients with:

- Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
- Elevated cardiac biomarkers (troponin T or troponin I)
- New or presumably new ST-segment depression
- Signs or symptoms of heart failure or new or worsening mitral regurgitation
- High-risk findings from noninvasive testing
- Hemodynamic instability
- Sustained ventricular tachycardia
- PCI within 6 months
- Prior CABG
- High-risk score, e.g. TIMI
- Reduced left ventricular function [left ventricular ejection fraction (LVEF)] less than 40%.

Aggressive antithrombotic therapy followed by early invasive treatment strategy is required for these patients. Also a glycoprotein IIb/IIIa inhibitor (such as abciximab) may also be indicated.

Adjunctive Therapy

Nitrates

Mainly used for pain relief, for ongoing ischemia or as a venodilator in patients with pulmonary edema.

Beta-Blockers

Oral β-blockers should be used within the first 24 hours in those without evidence of heart failure, low cardiac output, shock, bradyarrhythmias, or conduction blocks and other conditions like asthma. Cardioselective agents without intrinsic sympathomimetic activity are preferred. Metoprolol (50–200 mg/day) is the most commonly used agent. Intravenous β-blocker is used (metoprolol 5 mg intravenously thrice a day), titrated to patient response, heart rate (avoid if HR < 50 beats/minute) and blood pressure (avoid if less than 100 mm Hg systolic). Its use is best limited to situations with ongoing chest pain or uncontrolled tachycardia or hypertension. Calcium channel blocking agents (diltiazem) may be used as alternative therapy in patients with contraindication to β-blockers.

Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme inhibitors have indirect anti-ischemic benefit by reducing ventricular workload. These drugs should be used within the first 24 hours of ACS in patients without hypotension. They are most beneficial in patients with pulmonary congestion and depressed left ventricular systolic function.

Statin Therapy

The primary role of these agents is in long-term secondary prevention by lipid control. They may have some additional advantage in the early phase of ACS. An agent like atorvastatin is initially used in a relatively high dose (40–80 mg), and the dose can later be decreased to achieve the target lipids (low-density lipoprotein < 70–100 mg/dL). Patients who are already on statin should be continued on it.

Supportive Therapy

Sedatives and laxatives are useful in the initial stage. Hyperglycemia, either stress-induced or due to preexisting diabetes, should be controlled preferably at near-normal levels. Routine medication taken by the patient prior to the ACS should be reintroduced as appropriate.

BIBLIOGRAPHY

1. Anderson JL, Adams CD, Antman EM, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013; 61(23): e179-e347.

by mansdocs.com

2. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-2619.
3. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23): 2999-3054.
4. Hochman JS, Sleeper LA, Godfrey E, et al. Should we emergently revascularize Occluded Coronaries for cardiogenic shocK: an international randomized trial of emergency PTCA/CABG-trial design. The SHOCK Trial Study Group. Am Heart J. 1999;137(2):313-21.

by mansdocs.com

CHAPTER

16

Heart Failure

Yatin Mehta, Mukesh Kumar Gupta

INTRODUCTION

Heart failure is a very common condition with high mortality and morbidity rates. Data from the Framingham heart study suggests that at 40 years of age, the lifetime risk for getting congestive heart failure (CHF) is 21% for men and 20.3% for women. The prevalence of heart failure is between 2% and 3% and may reach 10–20% in men and women respectively, older than 70 years.

Patients presenting with an acute deterioration in function are often admitted in intensive care unit (ICU). These patients are likely to benefit from treatment:

- Worsening pulmonary edema with respiratory failure.
- Acute myocardial ischemia.
- Acute hemodynamic compromise due to arrhythmias
- Severe complicating diseases, e.g. pneumonia.

DEFINITION OF HEART FAILURE

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection.

Definition of Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) is defined as new or worsening of signs and symptoms of heart failure that is progressing rapidly, whereby unscheduled medical care or hospital evaluation is necessary. It is also known as acute heart failure or acute heart failure syndrome, but most appropriate term is ADHF.

Heart failure may result from disorders of pericardium, myocardium, endocardium, heart valves, great vessels and certain metabolic abnormalities. Most patients with heart failure have symptoms due to impaired left ventricular (LV) myocardial function. It should be emphasized that heart failure is not synonymous with either cardiomyopathy or LV dysfunction.

Heart failure may be associated with a wide spectrum of LV function abnormalities which may range from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF.

Types of heart failure:

- Heart failure with reduced EF (HFrEF), also called systolic heart failure.
- Heart failure with preserved EF (HFpEF), also called diastolic heart failure.

Heart Failure with Reduced Ejection Fraction

The definition of HFrEF has varied with guidelines of left ventricular ejection fraction (LVEF) less than 35% or 40%.

The present guideline, HFrEF is defined as the clinical diagnosis of heart failure and EF less than 40%.

Heart Failure with Preserved Ejection Fraction

Several criteria have been proposed to define the syndrome of HFpEF. These include:

- Clinical signs or symptoms of heart failure.
  - Evidence of preserved or normal LVEF.

by mansdocs.com

– Evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization.

Studies have suggested that the incidence of HFpEF is increasing and that a greater portion of patients hospitalized with heart failure has HFpEF. In general population, patients with HFpEF are usually older women with history of hypertension, diabetes mellitus, obesity or coronary artery disease. Despite these associated cardiovascular risk factors, hypertension is the most important cause of HFpEF, with a prevalence of 60–80%, from controlled trials, epidemiological studies and heart failure registries.

ETIOLOGY

Heart failure is caused by a loss of a critical quantity of myocardial cells after injury to the heart from a number of causes. The most common etiologies are:

- Ischemic heart disease
- Hypertension
- *Cardiomyopathies*: Familial/genetic or nonfamilial/nongenetic, including acquired, e.g. myocarditis, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular carduimyopathy (ARVC), unclassified.
- *Drugs*: B-blockers, calcium antagonists, antiarrhythmics, cytotoxic agents
- *Toxins*: Alcohol, medication, cocaine, trace elements (Hg, Cu, arsenic)
- *Endocrine*: Diabetes mellitus, hypothyroidism or hyperthyroidism, Cushing's syndrome, adrenal insufficiency, excessive growth hormone, pheochromocytoma
- *Nutritional*: Deficiency of thiamine, selenium, carnitine, obesity cachexia.
- *Infiltrative*: Sarcoidosis, amyloidosis, hemochromatosis, connective tissue disease.
- *Others*: Chagas disease, HIV infection, peripartum cardiomyopathy, end-stage renal failure.

FUNCTIONAL CLASSIFICATION OF HEART FAILURE

Two working classifications for heart failure:

1. New York Heart Association (NYHA) classification
2. American College of Cardiology (ACC) or American Heart Association (AHA) stage of heart failure.

New York Heart Association focuses on exercise capacity and symptomatic status of disease.

New York Heart Association Classification

Class I: No limitation of physical activity; ordinary physical activity does not cause symptoms of heart failure.

Class II: Slight limitation of physical activity, comfortable at rest, but ordinary physical activities result in symptoms of heart failure.

Class III: Marked limitation of physical activity, comfortable at rest, but less than ordinary activity causes symptoms of heart failure.

Class IV: Unable to carry out any physical activity without symptoms of heart failure or symptoms of heart failure at rest.

ACC/AHA Stage of Heart Failure

Emphasizes the development and progression of disease.

Stage A: At high-risk for heart failure but without structural heart disease or symptoms of heart failure.

Stage B: Structural heart disease but without signs or symptoms of heart failure.

Stage C: Structural heat disease with prior or current symptoms of heart failure.

Stage D: Refractory heart failure requiring specialized interventions.

PATHOPHYSIOLOGY OF HEART FAILURE

- *Left ventricular remodeling*: Left ventricular remodeling is the principal mechanism for the progression of heart failure. The major function and morphologic feature of remodeling are an increase in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) with reduced EF as the most consistent feature. There is alteration in shape and geometry of ventricles.
- *Neurohormonal activation*: Neurohormonal activation occurs early in patients with reduced EF even before the symptoms of overt heart failure appear. Adrenergic, renin-angiotensin-aldosterone system (RAAS) and vasopressin are activated in patient with asymptomatic LV systolic dysfunction. In patient with overt heart failure, the neurohormonal activation is more severe. The activation of RAAS and adrenergic system is associated with myocyte hypertrophy, myocyte apoptosis and necrosis, fibroblast growth and increased fibrosis. There is also increased oxidative stress which produces cytotoxicity. Neurohormonal activation can promote

by mansdocs.com

atherothrombotic and inflammatory responses. There is also vascular remodeling associated with smooth muscle cell hypertrophy. Neurohormonal activation is also associated with increase in systemic vascular resistance, ventricular filling pressure and arterial stiffness, which may produce adverse effects on the cardiac performance.

DIAGNOSIS

History and Physical Examination

Despite advances in imaging technology and increasing availability of diagnostic laboratory testing, a careful history and physical examination remain the corner stone in the assessment of patients with heart failure.

History of duration of illness, presence of chest pain, physical activity, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, palpitation, syncope, anorexia, early satiety, weight loss or weight gain is important. History of any medication or discontinuation of prescribed medication, diet and any history of recent or frequent prior hospitalization due to heart failure is important.

Cardiovascular Examination

Examination of the pulse will reveal normal strength and regularity of pulse rate. Blood pressure in supine and sitting position should be taken. Wide pulse pressure may reflect adequacy of cardiac output, decreased blood pressure in sitting position may be consistent with volume depletion or excessive vasodilatation from medication.

Jugular venous pressure at rest following abdominal compression (hepatojugular reflux), if elevated, suggests congestion. Size and location of maximal apical impulse if enlarged and displaced suggests ventricular enlargement.

Presence of palpable heave and thrill suggests significant right ventricular dysfunction, pulmonary hypertension and valvular heart disease. Extra heart sounds and murmur on auscultation of the heart, such as S3 or S4 if presents, are associated with adverse prognosis. If murmur is present following acute myocardial infarction, it may be suggestive of ventricular septal defect or mitral regurgitation.

Respiratory Examination

Patients with heart failure have a high respiratory rate. These patients on auscultation usually reveal extensive fine crepitation, usually bilaterally and predominately at the lung bases. Presence of decreased breath sound may suggest pleural effusion. However, some patients have predominant wheeze due to edema of bronchial wall and this may cause diagnostic confusion. Such patients may be treated for both bronchospasm and pulmonary edema.

In the most severely affected and exhausted patients, the chest may be silent because of reduced tidal volume and this may cause diagnostic confusion. In this situation, a single dose of intravenous diuretic agent should be tried and if a response to diuretic therapy is there, it suggests heart failure.

Abdominal Examination

Look for hepatomegaly, tenderness, ascites and edema of abdominal wall or genitalia. If present, suggests fluid overload, pulsation of the liver can indicate tricuspid regurgitation.

General Physical Examination

Examination may often reveal signs of heart failure. Patient is usually tachypneic, sweating, has pallor, increased work of breathing, using accessory muscles of respiration. Peripheral edema is not present especially in first episode of heart failure. If peripheral edema is present, it does not necessarily mean that it is due to cardiac cause. In obese and elderly patients, edema may reflect peripheral rather than cardiac causes. Cool lower extremities may reflect inadequate cardiac output.

INVESTIGATIONS

Initial laboratory tests of patient presenting with heart failure should include complete blood count, urine analysis, serum electrolyte (including calcium, magnesium), blood urea nitrogen (BUN), creatinine, glucose, fasting lipid profile, liver and thyroid function test.

Diagnostic test for rheumatologic diseases, amyloidosis, pheochromocytoma, hemochromatosis or HIV is reasonable in patients presenting with heart failure in which there is a clinical suspicion of these disease.

In the *The Acute Decompensated Heart Failure National Registry (ADHERE)*, blood urine nitrogen of greater than 43 mg/dL was the single test predictor of hospital mortality. Hypotension in patient with heart failure is a sign of failing circulatory hemostasis and is associated with longer length of stay and increased in hospital and early post discharge mortality. Anemia (hemoglobin <13 g/dL in males and 12 g/dL in females) is also a poor prognostic marker.

by mansdocs.com

Electrocardiogram

Electrocardiogram (ECG) is more useful to look for the cause or precipitant of heart failure rather than for diagnosis. ECG signs of ischemia, acute myocardial infarction, LV hypertrophy or arrhythmia may point to the precipitating cause of heart failure. Presence of atrial fibrillation and new T-wave changes were also associated with diagnosis of heart failure.

Chest Radiography

Chest radiography is useful mainly in cases of diagnostic difficulty. It is helpful to rule out noncardiac causes of dyspnea. The chest radiograph findings of pulmonary venous congestion, interstitial edema were most commonly associated with heart failure.

Echocardiography

Echocardiography should be carried out in all cases of suspected heart failure. Echocardiography evaluation should address whether LVEF is reduced, left ventricle structure is abnormal and whether other structural abnormalities are present that could account for the clinical presentation. This information should be quantified including numerical estimates of EF measurement, ventricular dimensions, wall thickness, calculation of ventricular volume and evaluation for chamber geometry and regional wall motion abnormality (RWMA). Right ventricular size and function as well as atrial size and dimension should be measured. Anatomy of all valves and their abnormality should be evaluated in patient with heart failure. Mitral valve inflow pattern, pulmonary venous flow pattern and mitral annular velocity provide data about grading of diastolic dysfunction and LV filling and left atrial pressure.

Noninvasive imaging should be done for myocardial viability assessment in select situations when planning revascularization in heart failure patients with coronary artery disease. Magnetic resonance imaging should be done when myocardial infiltrative process is suspected for heart failure.

B-type Natriuretic Peptides

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide L (NT-proBNP) are biomarkers that assist in diagnosis of heart failure. BNP is mainly synthesized and secreted by ventricular myocardium due to myocardial wall stress. BNP is released into the circulation as a prohormone and cleaved into the biologically active 32 amino acid BNP and biologically inactive 76 amino acid NT-proBNP.

Half-life of BNP is 20 minutes, whereas NT-proBNP has half-life of 120 minutes, which explain why NT-pro BNP serum value is approximately six times higher that BNP value.

In the Breathing Not Properly trial, 1,586 patients presenting to emergency department (ED) with dyspnea were investigated. A cut-off value of 100 pg/mL was determined to rule out heart failure and with BNP cut-off value of more than 500 pg/mL, heart failure was likely.

In the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, level less than 300 pg/mL was found to be optimal to rule out heart failure. With level more than 900 pg/mL, heart failure was likely. Independent of their diagnostic value, several large studies have shown that BNP and NT-proBNP provide strong prognostic information for an unfavorable outcome (death, cardiovascular death, readmission) for patients with heart failure. Natriuretic peptide concentrations are increased in other cardiac and noncardiac causes.

Cardiac Causes

- Acute coronary syndrome
- Heart muscle disease including LV hypertrophy
- Valvular heart disease
- Pericardial disease
- Atrial fibrillation
- Myocarditis
- Cardiac surgery
- Cardioversion.

Noncardiac Causes

- Advanced age
- Anemia
- Renal failure
- Obstructive sleep apnea
- Severe pneumonia
- Pulmonary hypertension
- Pulmonary embolism
- Critical illness
- Sepsis
- Severe burns
- *Toxic*: metabolic insults including cancer chemotherapy and envenomation.

In these conditions, the BNP and NT-proBNP are usually moderately elevated and typically not in the range observed in acute heart failure.

by mansdocs.com

Biomarker of Myocardial Injury Troponin T or I

Abnormal concentration of cardiac troponin is found in patient with heart failure, even after without obvious myocardial ischemia, and frequently in those without underlying disease.

In chronic heart failure (CHF), elevation of cardiac troponins is associated with impaired hemodynamics, progressive LV dysfunction and increased mortality. In ADHF, elevated cardiac troponin levels are associated with worse clinical outcomes and mortality.

Acute coronary syndrome and troponin elevation provide the link between myocardial infarction and development of the heart failure.

INVASIVE EVALUATION

Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with ADHF and congestion with symptomatic response to diuretics and vasodilators.

Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in which the adequacy or excess of intraventricular filling pressures cannot be determined from clinical assessment. It is also indicated in selected patients who have persistent symptoms despite empiric adjustment of standard therapies, for example:

- whose fluid status, perfusion or systemic or pulmonary vascular resistance is uncertain.
- whose systemic pressure remains low, or is associated with symptoms, despite initial therapy.
- whose renal function is worsening with therapy.
- who require parental vasoactive drugs.
- who may need consideration for mechanical circulatory support or cardiac transplantation.

When ischemia may be contributing to heart failure, coronary angiography is reasonable for patient eligible for revascularization.

PRECIPITATING FACTORS FOR ADHF

It is important to determine the precipitating factors that may have led to deterioration of cardiac function. The most important factors include the following:

- Poor compliance with medications
- Arrhythmia, particularly atrial arrhythmia
- Fluid overload due to deterioration of renal function
- Myocardial ischemia
- Poorly controlled hypertension
- Anemia
- Intercurrent illness, particularly infection
- Excessive diuresis.

TREATMENT OF ADHF

Patients presenting with acute deterioration of cardiac function may require admission in an ICU for stabilization. The treatment includes relief of symptoms, treatment of pulmonary edema, hemodynamic stabilization, management of comorbidities and precipitating factors and the initiation of long-term therapy.

Oxygen

The patient should be in erect sitting position. High flow oxygen therapy should be administered to hypoxic patient with pulmonary edema. This should be guided by pulse oximetry, keep the SpO_2 more than 94–96%.

Strong evidence supports the use of noninvasive positive pressure ventilation (NIV) to treat acute cardiogenic pulmonary edema. Positive pressure ventilation reduces the work of breathing, reduces preload and afterload. NIV decreases intubation and mortality rates compared to conventional therapy with oxygen.

Morphine

Morphine sulfate has been used to treat ADHF on basis that it is a potent venodilator with additional anxiolytic properties and blunts the respiratory drive. Data from ADHERE registry suggest that the use of morphine is associated with increased risk of intubation and is independent predictor of mortality. Based on these data, morphine should be avoided in patient with ADHF.

Diuretics

Diuretics have been the mainstay of treatment of ADHF for past four decades. Loop diuretics, particularly furosemide are still widely used and are recommended for this indication. In ADHERE study, 89% of patients received intravenous diuretics. Patients who undergo aggressive diuresis are at an increased risk for worsening of renal function known as cardiorenal syndrome. High dose diuretics have a number of adverse effects in patients with heart failure which include the following:

- Activation of RAAS
- Increased arginine vasopressin level

by mansdocs.com

- Increased norepinephrine level
- Decreased glomerular filtration rate (GFR)
- Increased systemic vascular resistance
- Electrolyte disturbances.

As per ADHERE, patient with ADHF should not receive more than 40–80 mg furosemide per day and this dose should be reduced in patients with worsening renal function. Some patients with significant fluid overload not responding to loop diuretics may require thiazide diuretics, like metolazone. Thiazide diuretic is weak diuretic when used alone. They work by blocking sodium reabsorption in distal renal tubules resulting in a profound diuresis.

Vasodilators

Vasodilator therapy is widely used in the treatment of patients who have ADHF with symptoms and signs of congestion and normal or elevated blood pressure. This class of agents includes a diverse group of drugs (e.g. nitrates, nesiritide, nitroprusside), that produce multiple, similar hemodynamic changes to the failing circulatory system.

Nitroglycerin

Nitroglycerin is a potent vasodilator and a mild arteriolar vasodilator at higher doses. It mimics the effects of nitric oxide by stimulating guanylate cyclase leading to smooth muscle relaxation in the vascular wall. It reduces LV filling pressure, pulmonary congestion, wall stress and myocardial oxygen consumption without compromising cardiac output. At high dose, it may improve ischemia by inducing coronary artery dilatation and increasing collateral blood flow. Nitroglycerin has very short half-life and is given by continuous intravenous infusion with dose titrated according to response and patients blood pressure.

The initial infusion rate is 10 mcg/min and rate may be increased to 300 mcg/min to achieve desired effects. Most common side effects are headache, hypotension and tachyphylaxis if used for more than 48 hours. It should not be used if systemic blood pressure is less than 90 mm Hg.

Nesiritide

Nesiritide is a recombinant form of human BNP with balanced arterial, venous and coronary vasodilator property. It promotes vasodilatation, sodium and water excretion and improves diastolic filling, resulting in reduced cardiac filling pressures. Nesiritide has been approved by US Food and Drug administration (FDA) for use in patients with acute ADHF in whom systolic blood pressure is above 90 mm Hg. It is given by 2 mcg/kg intravenous bolus followed by 0.01 mcg/kg/min continuous intravenous infusion, usually for 24–48 hours. It may cause hypotension and some patients may not respond to nesiritide.

Nitroprusside

Nitroprusside has arterial vasodilator properties. It improves ventricular performance by decreasing all the major components of LV afterload: systemic vascular resistance, arterial stiffness and arterial wave reflectance. Nitroprusside is most beneficial for hypertensive patients or patients with elevated filling pressure and systemic arterial pressure of 100 mm Hg or greater. Initial dose of 0.10–0.20 mcg/kg/min is gradually increased as needed to attain the desired clinical and hemodynamic effects up to 4 mcg/kg/min. Side effects and toxicity is directly related to dose and duration of administration. Cyanide may accumulate with prolonged high dose of nitroprusside infusion producing lactic acidosis. It is a potent vasodilator, so direct arterial monitoring and central venous pressure (CVP) monitoring are mandatory.

Inotropic Agents

Positive inotropic agents are indicated in the presence of hypotension and end organ hypoperfusion with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses

Dopamine

Dopamine is agonist at both dopaminergic receptors and adrenergic receptors. At low dose (2–5 mcg/kg/min) it acts on dopaminergic receptors, resulting in renal and mesenteric vasodilatation but have minor effects on diuresis. A dose of 5–10 mcg/kg/min will cause β1 receptor activation with positive inotropic effect. At high doses more than 10 mcg/kg/min, it acts on α and β1 receptor causing vasoconstriction with increased risk of tachyarrhythmia. Both dopamine and dobutamine should be used cautiously in patients with heart rate above 100 beat/min. Use of high dose of dopamine is associated with excessive morbidity and mortality in ICU.

Dobutamine

Dobutamine is a β-adrenergic agonist that stimulates β1, β2 and α1 adrenergic receptors. It increases cardiac

by mansdocs.com

contractility by β1 and α1 effects, but because α1 adrenergic effect are generally counter balanced by the β2 action, there is generally little change in blood pressure. Dobutamine increases cardiac output but produces only modest changes in LV filling pressures and virtually no increase in blood pressure. The usual dose of dobutamine is 2.5–15 mcg/kg/min. Short term infusion is often extremely effective in ADHF when systolic blood pressure is more than 100 mm Hg.

Milrinone

Milrinone is a type III phosphodiesterase inhibitor that produces dose-dependent increased cardiac output and decrease of LV filling pressure as a result of its positive inotropic, positive lusotropic and peripheral vasodilator actions. Despite these theoretical advantages, myocardial ischemia has been provoked by these agents and marked hypotensive episodes have been observed. It is used as 50 mcg/kg over 10 minutes as a loading dose followed by 0.375–0.75 mcg/kg/min as a maintenance infusion. The dose should be adjusted in patient with decrease renal clearance.

Levosimendan

It is a pyridazinone dinitrile derivative molecule that exerts positive inotropic effects by increasing the sensitivity of the cardiomyocyte contractile apparatus to intracellular calcium. It is a powerful opener of ATP-sensitive potassium channels causing peripheral arterial and venous dilation, leading to a reduction of peripheral vascular resistance and cardiac afterload. These processes result in a significant increase of cardiac output through its combined positive inotropic and peripheral vasodilation properties. The dose of levosimendan is 0.05–0.2 mcg/kg/min continuous intravenous infusion for 24 hours as it has active metabolites with long half-life.

Vasopressin Antagonist

Vasopressin levels are inappropriately high in both acute and CHF. Along with activation of sympathetic nervous system and RAAS, nonosmotic release of vasopressin is thought to represent a maladaptive response that is central to pathophysiology of heart failure. Vasopressin antagonists like conivaptan is used by intravenous route, while tolvaptan, used by oral route has been investigated in acute or CHF. Although these agents are associated with greater net fluid loss than placebo and normalization of serum sodium, they have not been associated with improved outcome.

Neurohormonal Blockade

Decline in cardiac output leads to activation of various neurohormonal cascades as compensatory process. These include activation of the sympathetic nervous system and RAAS axis. Increased concentrations of catecholamine, angiotensin II, vasopressin, atrial natriuretic peptide or BNP and endothelin are seen. Although the short- and long-term results of these processes often are helpful, the long-term consequences are more problematic. The proper use of neurohormonal blocking agents in the acute setting is thus difficult.

Beta-blocker

Patients who come to the hospital with ADHF should receive same dosage of beta-blocker if they are not in cardiogenic shock. If the exacerbation is mild with fluid overload being the main issue, the home dosage of beta-blocker can be maintained. If the exacerbation is more severe, then it is reasonable to reduce the dosage in half until perfusion is improved. The sickest patients may need withdrawal of beta-blocker. Patients with ADHF, who have either not been on beta-blocker therapy or who have not been compliant with beta-blockers, should not be restarted beta-blocker therapy acutely. An analysis of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry and Carvedilol or Metoprolol European Trial (COMET) demonstrated a longer hospital length of stay and a higher risk of death in whom beta-blocker therapy was discontinued or the dose reduced as compared to those in whom beta-blocker was continued or therapy with beta-blocker initiated. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, beta-blocker therapy reduced the risk of death and hospitalization in the subgroup of patients with recent or recurrent decompensation. These data suggest that all patients with ADHF should continue to be treated with beta-blockers unless specifically contraindicated.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting-enzyme inhibitors (ACE)-I were the first class of drugs, shown to improve outcome in patients with advanced heart failure. They have been

by mansdocs.com

shown to improve survival when started in hospitalized patients with refractory heart failure. They should be initiated at low dose in patient with low blood pressure. In patients who undergo aggressive induced diuresis, there is a risk of renal dysfunction and therefore the initiation of an ACE-I can be delayed until the patient is euvolemic. It is also to be remembered that initiation of ACE-I may cause an early rise in creatinine levels to approximately 25% above their baseline. The serum creatinine concentration is likely to stabilize after 4 weeks of therapy. Angiotensin receptor blockers (ARB) can be used in patients who develop a cough or angioedema with ACE-I.

Aldosterone Antagonists

Aldosterone antagonists significantly reduced mortality and hospitalizations for heart failure. Aldosterone antagonists should be administered to patients with symptomatic heart failure and left ventricle systolic dysfunction (LVSD) without renal dysfunction (serum creatinine level <2.5 mg/dL or a GFR >30 mL/min per 1.73 m^2 of body surface area) and without baseline hyperkalemia (>5 mEq/L). After initiating an aldosterone antagonist, serum potassium levels should be closely monitored, especially in patients with mild symptoms. The two available aldosterone antagonists, (i) spironolactone and (ii) eplerenone, differ in potency and in other effects including their antiandrogenic effects. Spironolactone is twice as potent as eplerenone as an aldosterone antagonist, but spironolactone also produces gynecomastia in 7% of men when administered at a dose of 25 mg daily, a side effect not seen with eplerenone. The agents have been tested in different populations, spironolactone in patients with severe heart failure and eplerenone in patients with mild heart failure and in patients with post-myocardial infarction.

Landmark trials including Randomized Aldactone Evaluation Study (RALES), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) demonstrated that aldosterone antagonism is indicated in all patients with LVSD and symptomatic heart failure and in patients following a recent myocardial infarction who develop LVSD with either signs of heart failure or concomitant diabetes.

Ultrafiltration

When diuretic resistance develops, ultrafiltration is an alternative approach for effective fluid removal. The Ultrafiltration Versus Intravenous Diuretics For Patients Hospitalized for ADHF (UNLOAD) trial enrolled 200 patients with ADHF and showed that ultrafiltration compared with diuretics increase weight loss at 48 hours, decreases the need for vasoactive drug and reduces rate of readmission to hospital at 90 days. Ultrafiltration offers the potential of greater volume and sodium removal as compared with conventional therapies in a more expeditious manner. Ultrafiltration should be considered in volume-overloaded patients who have responded poorly to loop diuretics.

Management of Atrial Fibrillation in Heart Failure Patients

Atrial fibrillation is common among patients with severe heart failure and is associated with higher mortality and an increased risk of hospitalization for heart failure. Rapid ventricular rate responses to atrial fibrillation may worsen LVSD and heart failure symptoms and in some cases, constitute the primary cause of the LVSD. Atrial fibrillation also increases the risk of thromboembolic events, especially stroke. Strategies to convert and maintain sinus rhythm in patients with atrial fibrillation and LVSD are frequently unsuccessful, whether using antiarrhythmic medications (e.g. amiodarone, dofetilide, etc.) or performing electrophysiologic interventions (including atrial fibrillation ablation). Thus, ventricular rate control and anticoagulation are critical. Although strict rate control (<80 beats/min at rest and <110 beats/min with exercise) yielded equivalent outcomes to rhythm control, recent data in patients with normal systolic function suggest that lenient resting rate control (<110 beat/min at rest) may provide equivalent or even superior benefit. It is not known if these observations about lenient rate control can be extended to patients with LVSD. Beta-blockers are more effective than digoxin in blocking exercise-induced increases in ventricular rate, although the combination of these agents may be especially efficacious. Calcium channel blockers (CCBs) should be avoided as ventricular rate-controlling agents in patients with LVSD. The primary indication for antithrombotics in heart failure patients is to prevent thromboembolic events associated with atrial fibrillation. Warfarin anticoagulation [international normalized ratio (INR 2–3)] decreases the thromboembolic risk in patients with atrial fibrillation and $CHADS_2$ scores greater than or equal to two. Heart failure patients with nonvalvular atrial fibrillation may be considered for alternative therapies other than warfarin. Newer agents include dabigatran (a direct thrombin

by mansdocs.com

inhibitor) and rivaroxaban and apixaban (direct factor Xa inhibitors). Compared with warfarin, they appear to be more efficacious (preventing stroke and systemic embolism), safer (causing less major and intracerebral hemorrhage) and more convenient (obviating the need for monitoring anticoagulation). These newer agents will likely replace warfarin in many patients in the future. However, regardless of the antithrombotic agent, the risk of bleeding appears to increase with age, renal dysfunction and through a variety of drug interactions.

ANEMIA

Anemia is common in patients with severe heart failure symptoms. The anemia is poor prognosis indicator of heart failure. Multiple factors contribute to anemia of heart failure, including decreased erythropoietin production due to kidney injury, ACE-I also inhibit erythropoietin production, increased level of proinflammatory mediators, gastrointestinal blood loss due to antiplatelet drugs as well as iron deficiency. Blood transfusions, however, do not improve outcome. Blood transfusion have myriad of deleterious effects including immune dysfunction and activation of inflammatory and coagulation pathways, increased risk of infection, acute lung injury, deep venous thrombosis, myocardial infarction, multiorgan failure and death. This anemia is often associated with blunted erythropoietin production and defective iron supply, and a small trial has demonstrated that treatment with subcutaneous erythropoietin and intravenous iron appears to improve symptoms, LVEF and renal function. Randomized controlled trials of intravenous iron in patients with heart failure and iron deficiency improved quality of life and functional capacity but showed no improvement in mortality. Administration of darbepoetin in anemic patients with heart failure has shown nonsignificant reductions in mortality and morbidity. No controlled clinical trials have studied transfusion in patients with heart failure, but transfusion adversely affects outcomes in other, critically ill anemic patients.

MECHANICAL CIRCULATORY DEVICES

In few hypotensive heart failure patients, poor perfusion state persists that does not improve with vasopressors and inotropic support. In these patients, mechanical circulatory devices may be needed. These devices are the following one:

Intra-Aortic Balloon Pump Counter-pulsation

Intra-aortic balloon pump (IABP) is the oldest technology in current use for mechanical support. Its first successful clinical use was reported by Kantrowitz and colleagues in 1968 in a patient with cardiogenic shock following a myocardial infarction.

Intra-aortic balloon pump is effective in a various clinical situations:

- In cardiogenic shock following myocardial infarction
- Circulatory support in the perioperative cardiac surgery period
- High-risk percutaneous coronary intervention
- As a bridge treatment for heart transplant.

The physiological theory behind aortic counterpulsation is that the balloon deflates during ventricular diastole, augments antegrade coronary perfusion and balloon deflates during ventricular systole and decreases resistance to ejection. These effects result in decreased myocardial wall stress, increased stroke volume, cardiac output and myocardial oxygen consumption.

Optimal IABP performance is dependent on multiple factors including the position of balloon in descending thoracic aorta, the balloon displacement volume, the relationship of balloon to aortic diameter, the inflation or deflation timing and hemodynamic variable such as circulating blood volume, blood pressure and vascular resistance.

Complications

Thrombocytopenia, vascular compromise, distal embolization, bleeding and infection are the complications.

Contraindications include, significant aortic regurgitation, active infection, advanced aortoiliac disease and coagulopathy.

Extra Corporeal Membrane Oxygenation

Extra corporeal membrane oxygenation (ECMO) uses conventional cardiopulmonary bypass technology to support the circulation with continuous nonpulsatile cardiac output and extra corporeal oxygenation. ECMO can be provided via a venous arterial cannulation that provides both circulatory and respiratory support. Venovenous cannulation can also be done, but it provides only respiratory support. Circuit consists of a venous reservoir, a centrifugal pump, a membrane oxygenator, pre- and post-membrane oxygen monitors and a rewarming circuit. In adults, right atrium and aorta are used for cannulation in operating room. The femoral vein and femoral artery are

by mansdocs.com

used for percutaneous insertion. ECMO is used in patients with respiratory and circulatory collapse, but its use is limited by the need for aggressive anticoagulation, full time perfusionist support and help of surgeon for placement of the cannula. Long-term support is complicated by a systemic inflammatory state that is seen with cardiopulmonary bypass and may include multiorgan system failure, resistant vasoplegia, coagulopathy and stroke. The use of ECMO in acutely decompensated patients with CHF has been limited. Therefore, it appears that the optimal use of ECMO in the nonoperative setting is to provide short-term circulatory support when shock persists despite IABP and maximal pharmacological support.

VENTRICULAR ASSIST DEVICES

Ventricular assist devices (VAD) are mechanical blood pumps that serve to either augment or replace the function of either the left or right ventricle. They are currently used for three purposes:

1. A bridge to myocardial recovery in acute ventricular failure.
2. A bridge to heart transplantation in chronic ventricular failure.
3. As permanent therapy for end-stage CHF.

The primary indication for VAD support is refractory heart failure, usually defined by cardiac index less than 2.0 L/min/m^2, a pulmonary capillary wedge pressure more than 20 mm Hg and a systolic blood pressure of less than 80 mm Hg despite pharmacologic agent and IABP. Most currently available devices are surgically implanted and require cardiopulmonary bypass for implant. Percutaneous VAD are in development phase. Currently, only one device (TandemHeart) is FDA approved and is in use. Other devices are undergoing trials.

TandemHeart

The TandemHeart device (cardiac assist, Pittsburgh, Pennsylvania) is a percutaneous VAD. The TandemHeart largely serves to unload the left ventricle providing a bypass circuit drawing blood from the left atrium and perfusing into descending aorta via a centrifugal pump independent of native heart rhythm. Inflow into pump is provided through a 21 Fr polyurethane transseptal cannula with a large end hole at its distal tip and 14 side holes to facilitate decompression of left atrium. The output is delivered via a 16–18F cannula to the femoral artery. The device provides up to 5 L/min of blood flow, it is not gated to the patient native rhythm and does not preclude the use of concomitant IABP.

Contraindications of TandemHeart Device

- Advance right ventricular failure
- Ventricular septal defect
- Aortic insufficiency
- Severe peripheral vascular disease.

Complication of TandemHeart Device

- Puncture of aortic root, coronary sinus and posterior free wall of right atrium
- Thromboembolism
- Systemic hypothermia
- Cannula dislodgment
- Bleeding
- Infection.

Impella Recover

The Impella Recover percutaneous VAD (Abiomed, Danvers, MA) is a micro-axial system that can be used for either left or right ventricle assist to provide short-term circulatory support for several days. The device comes in two sizes, (i) the LP 2.5 with a 12 Fr pump diameter capable of 2.5 L/min of flow and (ii) LP 5.0 with 21 Fr diameter that can provide up to 5 L/min, both systems are mounted on a 9 Fr pigtail catheter. The inflow cannula with its pump is inserted across the aortic valve under fluoroscopic guidance. The device sits across the aortic valve and draws blood through a distal port from the ventricle. Thereby actively unloading the ventricle blood is then pumped into aorta through a proximal port in ascending aorta.

Contraindications

- Mechanical prosthetic aortic valve
- Aortic valve stenosis or calcification
- Moderate to severe aortic insufficiency
- Severe peripheral vascular disease.

Complications

- Aortic valve injury
- Arrhythmia
- Bleeding, hemolysis
- Thrombocytopenia
- Limb ischemia and vascular injury.

by mansdocs.com

Continuous Aortic Flow Augmentation

The continuous aortic flow augmentation, Cancion system, (Orqis, Lake Forest, CA) is unique among current circulatory devices, it does not provide direct augmentation of cardiac output but rather recirculates arterial flow into the descending aorta drawn from the iliac artery. In low output syndromes, decreased aortic flow may stimulate downstream renal and vascular signals that lead to renal dysfunction and increase in vascular resistance. These signals may be the result of endothelial dysfunction and impaired nitric oxide induced by a reversal of flow along the aortic walls. By providing modest (1.5 L/min) continuous antegrade aortic flow and conserving forward flow during the entire cardiac cycle, vasodilatation may be improved in downstream vascular beds with subsequent falls in systemic vascular resistance and pulmonary capillary wedge pressure.

The Cancion system consists of a magnetically levitated centrifugal pump (priming volume, 32 mL) that draws blood from a percutaneously placed 12 Fr cannula in the left common femoral artery and returns blood to the descending aorta via a pigtail outflow cannula in the right femoral artery placed distal to the subclavian artery origin. The continuous output is superimposed on the pulsatile native cardiac output without gating. The entire blood capacity of the system is 108 mL. Systemic anticoagulation with intravenous heparin is required.

Implantable Cardioverter-Defibrillator

Patients with HFrEF predominantly die of either pump failure or sudden cardiac death caused by pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF). Implantable cardioverter-defibrillators (ICDs) are indicated for the primary prevention of sudden cardiac death in patients with at least 1-year life expectancy who are on maximal medical therapy with the following:

- Left ventricular ejection fraction less than 30% and NYHA Class I to III CHF following a myocardial infarction
- Left ventricular ejection fraction less than 35% and NYHA Class II or III CHF from ischemic or nonischemic causes.

Implantable cardioverter-defibrillators are generally not indicated in patients with NYHA Class IV CHF because these patients frequently die of pump failure.

CARDIAC RESYNCHRONIZATION THERAPY

Patients with severe LV dysfunction and a left bundle branch block (LBBB) have significantly higher mortality than those without LBBB. This higher mortality may be caused by dyssynchrony of LV contraction. Resynchronization therapy with a biventricular pacemaker (first lead placed in the right ventricular apex and the second placed in the lateral wall of the left ventricle via the coronary sinus) has been shown to improve symptoms of heart failure, as well as mortality, in patients with:

- Left ventricular ejection fraction less than or equal to 35%, NYHA Class III or IV CHF despite optimal medical therapy from ischemic or nonischemic causes and a QRS greater than 120 milliseconds.
- Left ventricular ejection fraction less than or equal to 30%, QRS greater than or equal to 150 milliseconds and NYHA Class II CHF despite optimal medical therapy.

DISCHARGE PLANNING AND OUTPATIENT CARE

The most important aspect of acute care may be arranging close and careful follow-up. Thought should be given to the cause of decompensation for each individual patient, and a plan to avoid recurrence should be put in place so that future hospital admissions can be prevented. Education on managing their disease at home, medication management and nutrition are paramount. Patients and their families need to understand the dietary and fluid restrictions. Patients should be counseled if they gain more than 1.5 kg in 1 day or 2.5–3 kg in 1 week, they should call their cardiologist immediately for instructions regarding diuretic titration. It has clearly been shown that frequent communication between the patient and the caretaker improves outcomes. It is also very important to realize, both in the acute setting and chronically, that patients who are difficult to manage should be considered for referral to a tertiary care center. There are many options for patients with advanced heart failure, including mechanical assist devices and transplantation, which have dramatically improved the outcomes in these patients in the long term. These patients should be referred before damage to the kidneys or other organs has been prolonged. Renal insufficiency and prolonged hepatic congestion, leading to cirrhosis, increase the risk of mechanical support and transplantation, so it is better to err on the side of referring too early.

by mansdocs.com

SUMMARY

Heart failure is the most common cause of cardiovascular hospital admission. Not only is CHF a major cause of morbidity and mortality in the general population, but it also consumes 1–2% of the total health-care resources. The total costs for heart failure care have increased, considerably over the past 10 years. The most effective approach for preventing heart failure hospitalizations is a combination of improvement in management of these patients while they are in the hospital and comprehensive post discharge care. Decreasing the length of hospitalization can increase readmission rate, so optimization of inpatient and outpatient care is essential. This should include ensuring adequate diuresis before discharge, optimization of medical treatment for heart failure during the hospitalization, thorough patient education before discharge and close outpatient follow-up.

BIBLIOGRAPHY

1. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation 2013;128:e240-e327.
2. Brown JR, Gottlieb SS. Acute decompensated heart failure. Cardiol Clin. 2012;30(4):665-71.
3. Chang AM, Maisel AS, Hollander JE. Diagnosis of heart failure. Heart Fail Clin. 2009;5(1):25-35.
4. Hiestand BC. Circulatory assist devices in heart failure patients. Heart Fail Clin. 2009;5(1):55-62.
5. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovascular Pathology. 2012;21(5):365-71.
6. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.
7. Neuenschwander JF 2nd, Baliga RR. Acute decompensated heart failure. Crit Care Clin. 2007;23(4):737-58.
8. Nicklas JM, Bleske BE, Harrison RV, et al. Heart failure clinical problem and management. Prim Care Clin Office Pract. 2013;40:17-42.
9. HFSA 2010 Comprehensive Heart Failure Practice Guideline. Lindenfeld J, Albert NM, et al. J Card Fail 2010;16: e1-194.

by mansdocs.com

CHAPTER

17

Cardiac Arrhythmias in ICU

Supradip Ghosh

OBJECTIVES

- To understand various waves and intervals of normal electrocardiogram (ECG)
- To learn the basic pathophysiology of tachyarrhythmias
- To learn about the normal conduction system and mechanisms of bradyarrhythmias
- To recognize common arrhythmias seen in the intensive care unit (ICU) and learn the management strategies for these arrhythmias.

INTRODUCTION

Critically ill patients frequently have underlying cardiovascular disease and are frequently subjected to ischemic, metabolic and neurohumoral stressors. In a prospective multicenter European study, prevalence of sustained arrhythmias in general ICU population was estimated to be 12%. Ventricular arrhythmias were found to increase risk of death and neurological sequelae.

NORMAL ECG WAVES AND INTERVALS

Normal ECG waves and intervals have been described in Figure 1.

NORMAL SINUS RHYTHM (FIG. 2)

Mechanisms of Tachyarrhythmias

Abnormal automaticity: Impulse generation is from cells that are not normally arrhythmogenic.

Triggered automaticity: This is due to secondary depolarization that arise during repolarization or immediately after repolarization.

Re-entry: This is the most common mechanism of tachyarrhythmia. The genesis and propagation of the arrhythmia requires the presence of an area of slow conduction, an anatomical or functionally separate path of conduction and unidirectional block.

SUPRAVENTRICULAR TACHYARRHYTHMIAS

Diagnosis

- A rhythm strip if unstable or a 12-lead ECG

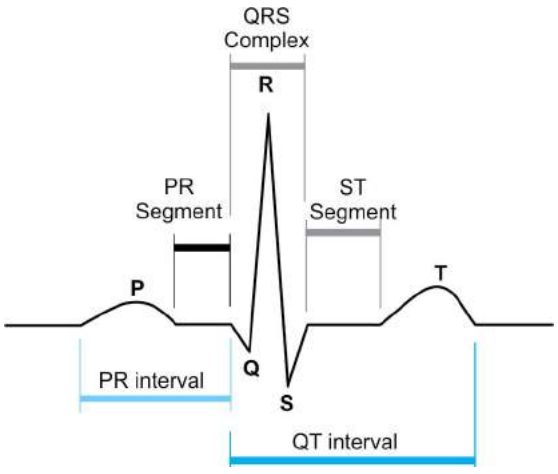


Fig. 1: Electrocardiographic waves and intervals.
Keys: PR interval, 120–200 ms (1 small square = 40 ms); QRS duration, <-120 ms; QT interval, 440 ± 40 ms

by mansdocs.com

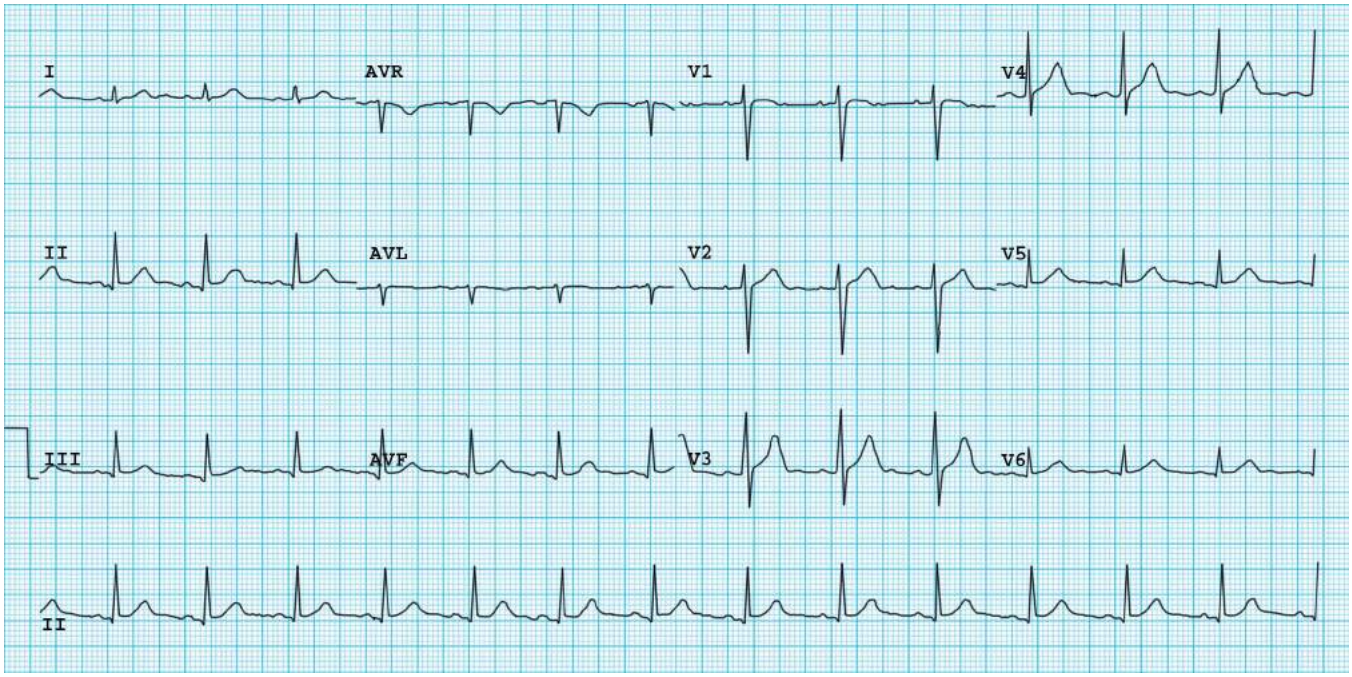
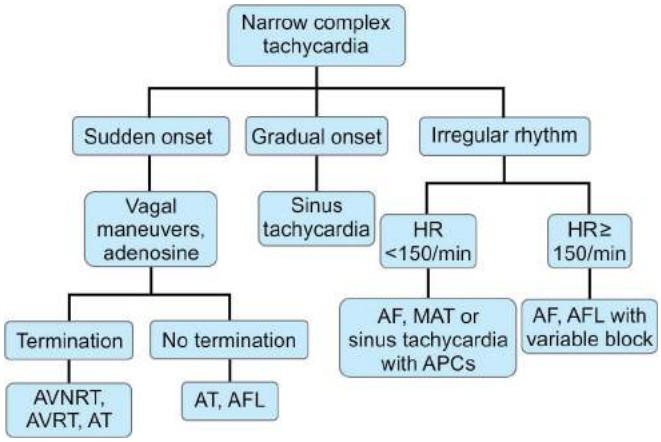


Fig. 2: Normal sinus rhythm. Rate: 60–100 beats/min; P wave preceding every QRS complex; Normal PR interval, QRS duration and QT interval; Sinus tachycardia: rate > 100 beats/min; Sinus bradycardia: rate < 60 beats/min.

Flowchart 1: Supraventricular narrow QRS complex tachycardia (diagnosis).



(AVNRT: Atrioventricular nodal re-entrant tachycardia; AVRT: Atrioventricular re-entrant tachycardia; AT: Atrial tachycardia; AFL: Atrial flutter; AF: Atrial fibrillation; APCs: Atrial premature contractions; MAT: Multifocal atrial tachycardia; HR: Heart rate).

- *Look for*:
  - Rate and regularity of RR interval
  - Presence of P wave
  - P wave morphology
  - QRS duration and morphology
  - Response to therapy
- Follow the algorithm shown in Flowchart 1.

SINUS TACHYCARDIA

- Sinus tachycardia is an appropriate cardiac response to physiological events
- Gradual onset
- Common etiologies—fever, sepsis, left ventricular (LV) failure, pulmonary embolism, hyperthyroidism, etc.

ECG Features (Fig. 3)

- Regular heart rate more than 100 beats/min (does not exceed 220 beats/min minus patient's age)
- P wave always precedes QRS complex.

Treatment

- No specific antiarrhythmic therapy recommended except in inappropriate sinus tachycardia in the absence of precipitating cause where selective sinus node blocking agent ivabradine may be considered.
- Treat the underlying cause.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common pathological supraventricular arrhythmia in the ICU setting. It is seen in the setting older age, male sex, hypertension, ischemic heart disease, thyrotoxicosis, alcohol binging (Holiday

by mansdocs.com



Fig. 3: Sinus tachycardia.



Fig. 4: Atrial fibrillation.

heart syndrome) and pulmonary embolism. It may be acute in onset, usually in younger patients when the patient is aware of its onset (palpitation) or more chronic, gradual in onset like sinus tachycardia and patient is not aware of its onset.

Complications of AF include hypotension, ischemic, diastolic heart failure (rate related and loss of atrial pumping) or systemic emboli.

Classification

- First detected
- Paroxysmal (up to 7 days)
- Persistent (> 7 days)
- Permanent (> 1 year).

Because AF may be asymptomatic, the "first detected episode" should not be regarded as true onset of arrhythmia.

ECG Features (Fig. 4)

- No definite P wave, rapid oscillations or fibrillatory F waves
- Irregular RR interval
- Ventricular rate is determined by the degree of atrioventricular (AV) conduction (100–220 beats/min)
- QRS is usually narrow, unless there is a pre-existing bundle branch block or conduction through an accessory pathway or an aberrant conduction (Ashman's phenomenon).

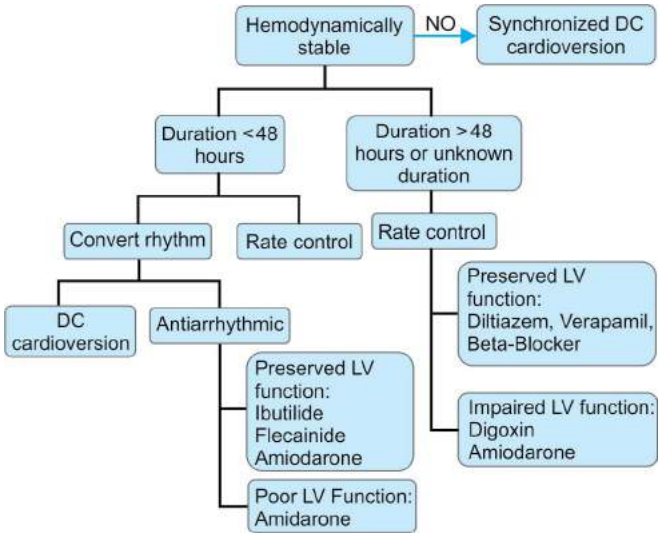
Management (Flowchart 2)

Rate Control

Ventricular response rate needs to be reduced to alleviate symptoms of palpitation, prevent tachycardia-induced cardiomyopathy and also to prevent hemodynamic compromise. Goal is to achieve a resting heart rate of 80 beats/min and maximum heart rate less than 110 beats/min after 6-minute walk test [atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial data]. All reversible causes of AF must be treated and electrolyte imbalances must be corrected. Certain factors like underlying LV systolic function, associated accessory pathway, underlying disease and rate of onset of particular agent need to be considered before choosing a drug for control of ventricular rate.

by mansdocs.com

Flowchart 2: Management of supraventricular tachycardia.



Atrioventricular nodal blocking agents (beta-blockers and nondihydropyridine calcium channel blockers) are commonly used agents. Diltiazem is often the first agent chosen; as it is well tolerated, acts rapidly and can be administered as continuous infusion (Table 1). AV nodal blocking agents must be avoided if there is a suspicion of associated accessory pathway, as AV blocking results in uncontrolled ventricular rate via the accessory pathway. Amiodarone is the preferred agent in this situation. Amiodarone may also be considered in patients with underlying LV dysfunction. In patients with underlying LV dysfunction, calcium channel blockers and beta-blockers should be avoided because of their negative inotropic effect. Digoxin may be considered in these patients despite its slow onset of action and potential adverse effects. Beta-blockers are the agents of choice in patients with thyrotoxicosis.

Rhythm Control

In hemodynamically unstable patients, urgent electrical cardioversion is indicated to achieve rapid control of the rhythm, irrespective of the duration of arrhythmia. Rhythm control (electrical or pharmacological) is also preferred in those patients for whom a shortened diastolic period may be detrimental (e.g. patient with mitral stenosis or hypertrophic cardiomyopathy) or in patients with associated accessory pathway. If the duration of AF is more than 48 hours or unknown, patient must be adequately anticoagulated before electrical or pharmacological cardioversion.

In patients with recent onset AF, sinus rhythm can be restored with direct current shock of as low as 100 J, but it is recommended that cardioversion be started with initial shock energy level of 200 J or more. In patient where duration of AF is not known, in obese patients or patients with emphysema, a higher energy level up to 300–360 J may be preferable.

If the AF is recent onset and hemodynamically stable, pharmacological cardioversion may be effective. This can be accomplished class IC agents like flecainide, class III agents like ibutilide or amiodarone and procainamide (Table 2). Class IC agents should not be used in the presence of coronary artery disease. Procainamide is the drug of choice in the presence of accessory pathway. Amiodarone, though not very efficacious in converting to sinus rhythm, is often preferred in critically ill patients because of its ability to control ventricular rate, a low likelihood of torsade de pointes, absence of negative inotropic effect and safety in the presence of structural heart disease. It needs to be administered through a control line.

Anticoagulation Strategies

Anticoagulation is mandatory if AF/atrial flutter (AFL) persists for more than 48 hours or if duration is unknown before cardioversion. In hemodynamically stable arrhythmias of more than 48 hours duration, rate control is achieved and patients are adequately anticoagulated for 3-weeks anticoagulation with warfarin before cardioversion [international normalized ratio (INR) 2–3]. Anticoagulation needs to be continued for 4 weeks after cardioversion.

Alternatively, a transesophageal echocardiography (TEE) guided approach may be considered, where patients are anticoagulated with heparin or low-molecular-weight heparin, followed by TEE to look for thrombus in left atrial appendages, before cardioversion. This is easy in an intubated patient. This approach shortens time to rhythm control. Anticoagulation with warfarin must be continued for next 4 weeks.

ATRIAL FLUTTER

Atrial flutter is the second most common pathological supraventricular arrhythmia. It is an organized regular rhythm, results usually from a re-entrant circuit around the tricuspid valve in the right atrium (typical flutter). Atypical flutter occurs in persons who have undergone cardiac surgery or cardiac ablation.

by mansdocs.com

Table 1: Drugs used for rate control in atrial fibrillation.

Drug	*Route*	*Dose*	*Onset*	*Adverse Effects*
Diltiazem	IV	0.25 mg/kg over 2 min, if no response additional 0.35 mg/kg after 15–20 min; followed by 5–10 mg/h infusion	2–5 min	Hypotension, bradycardia, heart block, deterioration of underlying heart failure
Verapamil	IV	5–10 mg over 2 min, addition 5–10 mg if no response	2–5 min	Same as diltiazem
Esmolol	IV	500 μ/kg over 1 min, followed by 50–200 μ/kg over 4 min; if no response repeat the same dose after 5 min. Infusion 50–200 μ/kg/min	2–3 min	Hypotension, bradycardia, deterioration of LV function, heart block, bronchospasm
Metoprolol	IV	2.5–5 mg over 2 min followed by repeat doses if necessary (up to 15 mg)	5 min	Same as Esmolol
Digoxin	IV	0.5–1 mg followed by 0.25 mg every 2–4 h (maximum 1.5 mg)	30–60 min	Bradycardia, AV block, increased automaticity—ventricular and atrial arrhythmias

(AV: Atrioventricular; IV: Intravenous; LV: Left ventricle).

Table 2: Drugs used for pharmacological cardioversion of atrial fibrillation.

Drug	*Route*	*Dose*	*Adverse Effects*
Flecainide	IV	1.5–2 mg/kg over 10–20 min; if no response infusion 1.5 mg/kg for 1 h, then 0.1–0.25 mg/kg over 24 h	Deterioration of LV function in the presence of structural heart disease, monomorphic VT
Ibutilide	IV	1 mg over 1 min, if no response additional 1 mg	QT prolongation, Torsade de pointes, hypotension
Amiodarone	IV	15 mg/min for 10 min, 1 mg/min for 6 h and 0.5 mg/min for 18 h. Supplemental infusion of 150 mg for 10 min in a case of breakthrough arrhythmias.	Hypotension, QT prolongation, gastrointestinal upset, constipation, phlebitis
Procainamide	IV	1,000 mg over 30 min followed by 2 mg/min infusion	QRS widening, torsade de pointes, worsening of LV failure (contraindicated if LVEF < 40%)

(IV: Intravenous; LV: Left ventricle; LVEF: Left ventricular ejection fraction; VT: Ventricular tachycardia).



Fig. 5: Atrial flutter.

ECG Features (Fig. 5)

- Characteristic saw tooth flutter wave with a rate of 280–300 beats/min
- Usually narrow QRS complex unless there is a pre-existing bundle branch block or conduction through an accessory pathway or an aberrant conduction
- Usually 2:1 AV nodal conduction results in a ventricular rate of 140–150/min. At this ventricular rate a heart rate, flutter waves may be obscured by T waves, making it difficult to distinguish from that of other supraventricular tachycardias. However, a heart rate of 150 beats/min is highly suggestive of this tachyarrhythmia

by mansdocs.com

- Patients with AV nodal disease or who are receiving AV node-blocking medications, the rate in atrial flutter may be slower than 140–150 beats/min and may be irregular like AF.

Management

Management is similar to AF except the fact that being a more organized rhythm, atrial flutter can be converted to sinus rhythm with energy level as low as 25–50 J, but 100 J (virtually being successful in all cases) is the preferred initial energy level.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Atrioventricular Nodal Re-entrant Tachycardia

Atrioventricular nodal re-entrant tachycardia (AVNRT) is a sudden onset, regular tachycardia, caused by re-entrant loop within atria and perinodal tissue. This is the most common form of paroxysmal supraventricular tachycardia (PSVT) comprising 50–60% of cases. It usually occurs in patients over 20 years of age and commoner in female sex. There is usually no associated structural heart disease.

ECG Features (Fig. 6)

- Regular, rapid ventricular rate ranging from 140 beats/min to 280 beats/min
- Usually narrow QRS complex, unless there is pre-existing bundle branch block or there is aberrant conduction
- Atrium is depolarized retrogradely, and P wave is usually buried.

Atrioventricular Re-entry Tachycardia

It is a sudden onset, re-entrant loop tachycardia, similar to AVNRT; however, unlike AVNRT one pathway of the loop is in the AV node and the other is outside the AV node (but adjacent to). It is the second most common form of PSVT, comprising of 30% of cases. Conduction may be orthodromic resulting in narrow QRS complex or antidromic resulting in wide QRS complex tachycardia.

ECG Features

- Regular tachycardia with rate of 150–250 beats/min
- In narrow complex—P wave after QRS complex
- In wide complex—P wave rarely observed.

Atrial Tachycardia

Atrial tachycardia (AT) is a sudden onset narrow complex tachycardia due to abnormal automaticity. Frequently associated with other comorbidities, e.g. postoperative congenital heart defect or digitalis toxicity (AT with AV block).

ECG Features (Fig. 7)

- Sudden onset, regular, narrow QRS complex, rate of 150–250 beats/min
- P wave morphology distinctly different from usual sinus P wave.

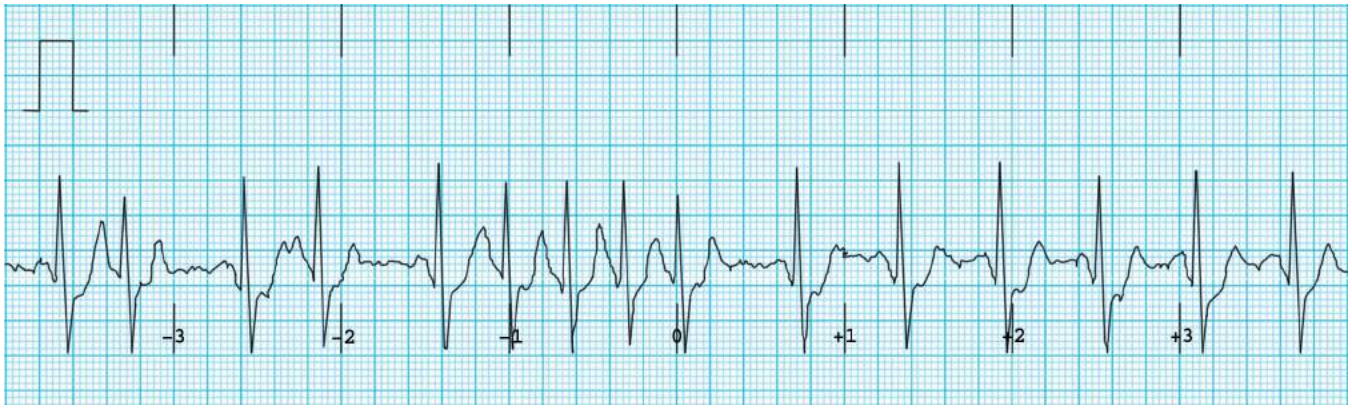


Fig. 6: Atrioventricular nodal re-entrant tachycardia.

by mansdocs.com

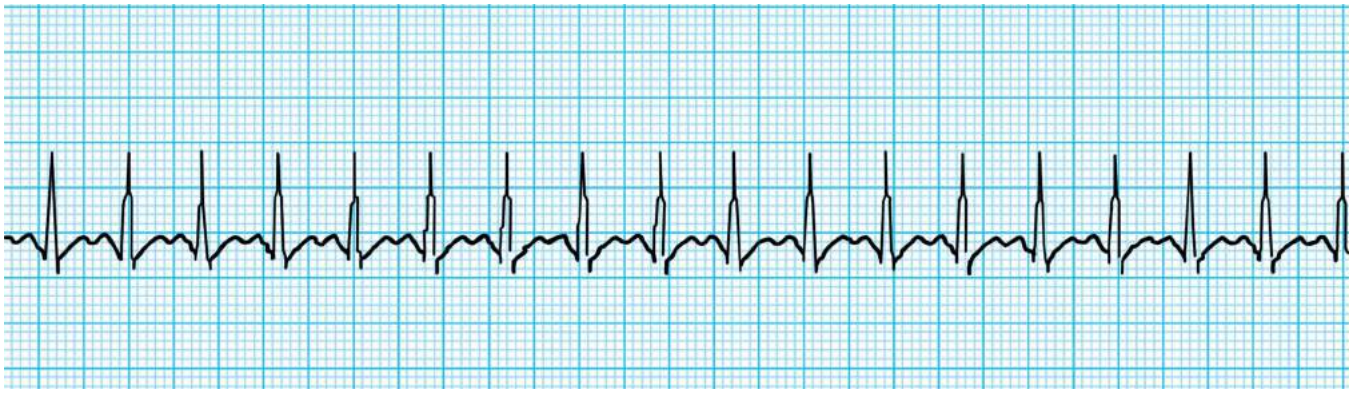
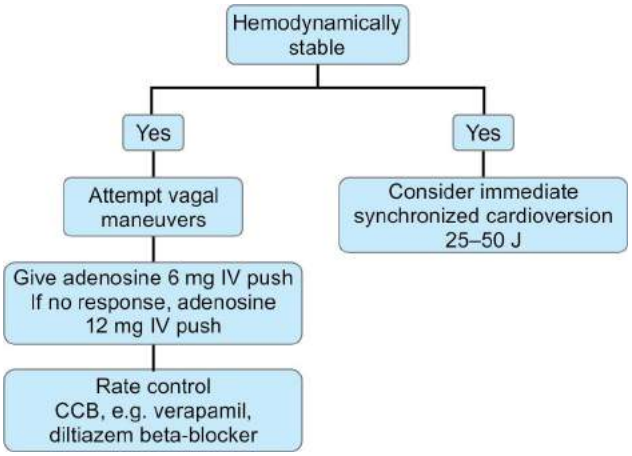


Fig. 7: Atrial tachycardia.

Management (Flowchart 3)

Flowchart 3: Management of paroxysmal supraventricular tachycardia.



(CCB: Calcium channel blocker).

Carotid Sinus Massage: Steps

- Ensure that there is no carotid bruit
- Continuous ECG monitoring
- Supine position
- Start with right carotid sinus—rotatory or steady pressure to the carotid artery at the level of 3rd cervical vertebra
- If no response, massage the left sinus
- Do not massage both carotids simultaneously.

Drugs

Adenosine

Adenosine acts rapidly on the AV node and causes complete AV blockade lasting for few seconds. It has a short half-life of 10 seconds, and it is to be given in rapid IV bolus (3–6 mg, another 6–12 mg 2–5 min later if necessary). It does not have negative inotropic effect and may be used in LV dysfunction or hypotension. Common adverse effects are flushing, bronchospasm, chest tightness. May provoke AF, AFL or rapid ventricular rate in the presence of accessory pathways. Heart transplant recipients are very sensitive to the drug (dose 1 mg). Metabolism of adenosine is delayed in the presence of methylxanthine derivatives, like aminophylline; therefore, lower dosage may be considered.

Nondihydropyridine Calcium Channel Blockers and Beta-Blockers

Alternative to adenosine but they are longer acting with potential side effects.

MULTIFOCAL ATRIAL TACHYCARDIA

Classically seen in patients with chronic obstructive pulmonary disease (COPD) with acute exacerbation. Multifocal atrial tachycardia (MAT) is also seen in patients with congestive heart failure and theophylline toxicity.

ECG Features (Fig. 8)

- Varying P wave morphology—three or more in same lead
- Varying RR interval.

Management

- Treatment of underlying cause
- Intravenous (IV) magnesium may decrease atrial automaticity. Diltiazem or beta-blockers may decrease the ventricular rate
- Amiodarone occasionally restores the rhythm to sinus.

by mansdocs.com



Fig. 8: Multifocal atrial tachycardia.



Fig. 9: Ventricular premature complex.

VENTRICULAR TACHYARRHYTHMIAS

Ventricular Premature Complexes

- Maybe found in normal healthy individual
- But may accompany cardiac conditions (e.g. ischemia), stimulants (e.g. caffeine), dyselectrolytemia (e.g. hypokalemia), hypoxemia, medications (e.g. tricyclic antidepressants, digoxin).
- *Monomorphic*: Identical premature ventricular complexes (PVCs) arising from single ectopic focus identical coupling interval.
- *Polymorphic*: PVCs arising from different foci with varying coupling interval.

ECG Criteria (Fig. 9)

- Wide QRS complex with a bizarre axis
- T wave polarity opposite to QRS complex
- Compensatory pause.

Treatment

- No specific antiarrhythmic drugs
- Beta-blockers are recommended in the setting of acute coronary syndrome
- Correction of underlying conditions, e.g. hypokalemia.

Ventricular Tachycardia

- More than or equal to three ventricular ectopic beats with rate more than 100 beats/min and often ranges between 130 beats/min and 170 beats/min
- Clue to diagnosis is AV dissociation, identified by presence of P wave (sometimes a Lewis lead or esophageal lead) and QRS complex at uncoupled rates, capture beat and fusion beat (Fig. 10).

Lewis Lead

ECG recorded with the right arm electrode applied to the right of the sternum at the second intercostal space, and the left arm electrode applied to the fourth intercostal space (Fig. 11). After recording, the tracing should be recorded in lead I.

Classification

- Duration of tachycardia

by mansdocs.com

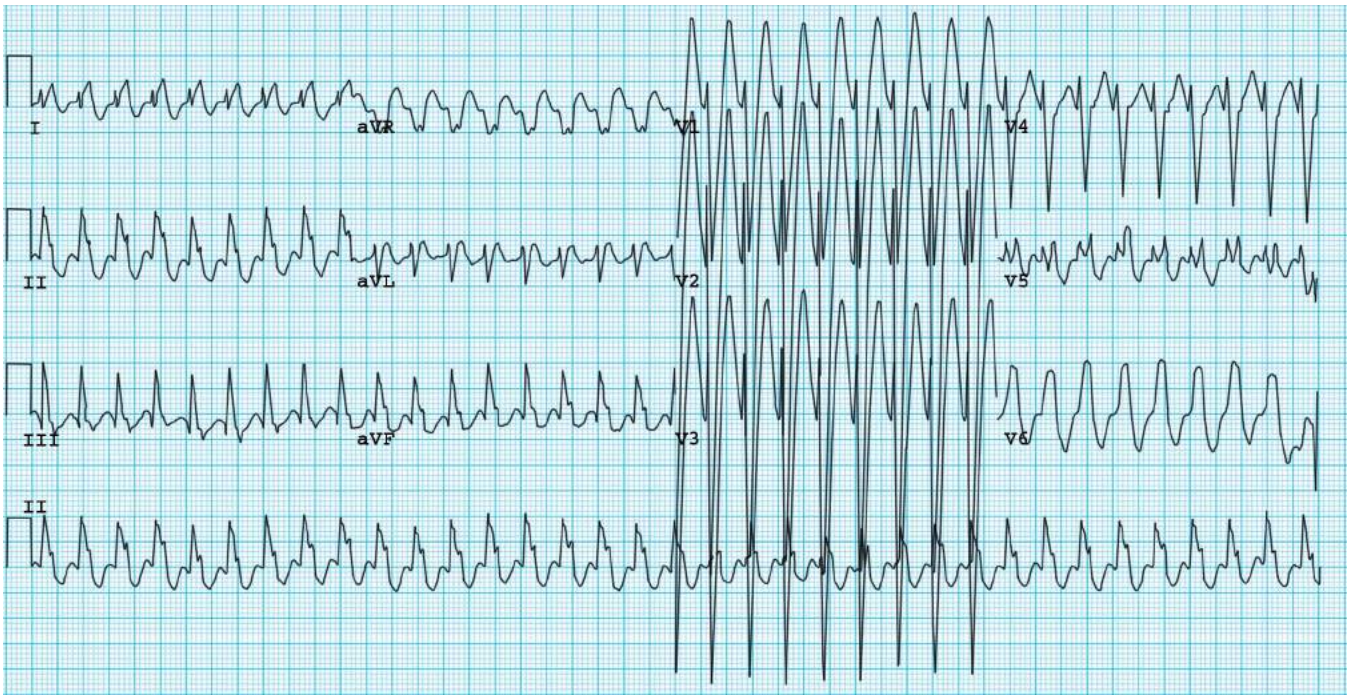


Fig. 10: Monomorphic ventricular tachycardia.

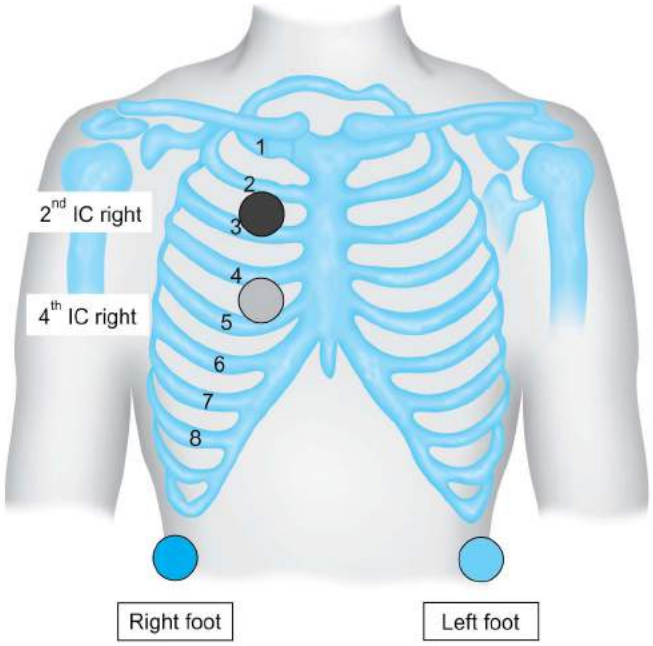


Fig. 11: Lewis lead placement.

  - Nonsustained—lasting for less than 30 ms
  - Sustained—lasting for more than or equal to 30 ms
- Morphologic
  - Monomorphic—identical PVCs
  - Polymorphic—varying PVC morphology
- Hemodynamic stability
  - Unstable—hypotension, angina, palpitation
  - Stable.

Differential Diagnosis of Wide Complex Tachycardia (Flowcharts 4 and 5)

- Ventricular tachycardia
- Supraventricular tachycardia with aberrant conduction (Ashman phenomenon)
- Supraventricular tachycardia with pre-existing bundle branch block
- PSVT or AF with conduction via accessory pathway.

Morphologic Criteria for Ventricular Tachycardia

Right bundle branch block morphology (dominant R wave in V1) (Fig. 12):

Appearance in V1–V2:

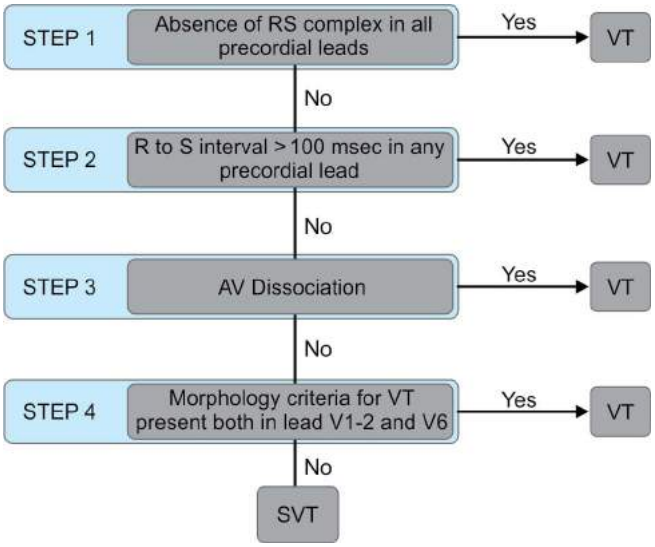
- Smooth monophasic R wave
- Notched downslope to the R wave—the taller left rabbit ear (= Marriott's sign)
- A qR complex (small Q wave, tall R wave) in V1

Appearance in V6:

- QS complex—a completely negative complex with no R wave
- R/S ratio less than one—small R wave, deep S wave.

by mansdocs.com

Flowchart 4: Brugada criteria ventricular tachycardia (VT) versus supraventricular tachycardia (SVT).



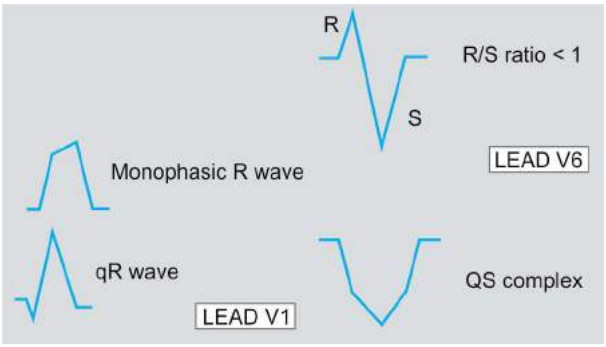


Fig. 12: Morphologic features of ventricular tachycardia with right bundle branch block (RBBB) pattern.

Left bundle branch block morphology (dominant S wave in V1) (Fig. 13):

Appearance in V1–V2:

- Initial R wave more than 30–40 ms duration
- Notching or slurring of the S wave (Josephson's sign)
- RS interval (time from R wave onset to S wave nadir) more than 60–70 ms.

Appearance in V6:

- QS waves in V6
- qR pattern.

Management

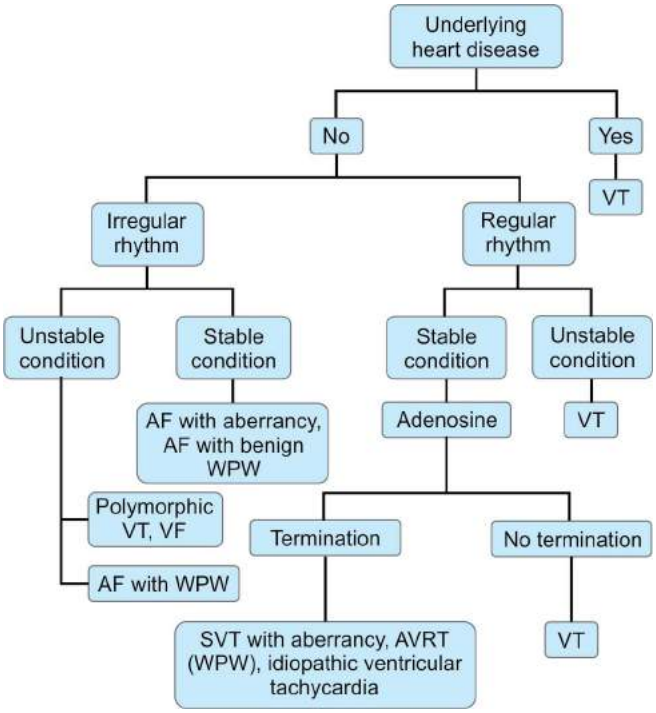
Hemodynamically unstable:

- Prompt defibrillation and efficient cardiopulmonary resuscitation (CPR) as per advanced cardiovascular life support algorithm. At least 200 J biphasic shock is to be delivered
- If ventricular tachycardia persists after three shocks, adrenaline (or vasopressin) and CPR are consider antiarrhythmic medication—amiodarone initial bolus followed by infusion is the preferred drug. In Torsade de pointes, consider magnesium sulfate.

Hemodynamically stable:

- Antiarrhythmic drug is to be administered after confirmation of diagnosis. Use of multiple antiarrhythmic

Flowchart 5: Diagnosis of wide complex tachycardia.



(AF: Atrial fibrillation; ARVT: Atrioventricular re-entrant tachycardia; SVT: Supraventricular tachycardia; VF: Ventricular fibrillation; VT: Ventricular tachycardia; WPW: Wolff-Parkinson-White syndrome).

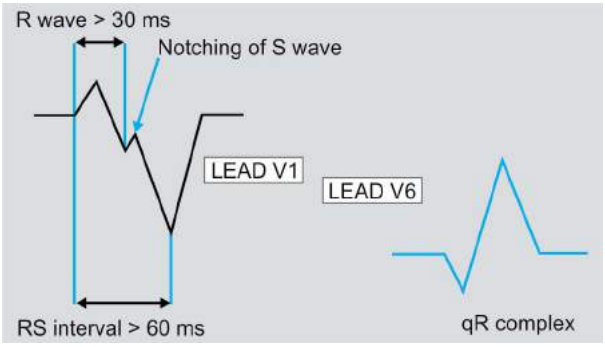


Fig. 13: Morphologic features of ventricular tachycardia with left bundle branch block (LBBB) pattern.

by mansdocs.com

drugs needs to be avoided. Consider cardioversion if initial agent selected is ineffective (Table 3)
- First-line drug—amiodarone, procainamide and, in some circumstances, lidocaine. Procainamide should be avoided in significant LV dysfunction (left ventricular ejection fraction < 40%) and in renal dysfunction (Table 4).

Polymorphic Ventricular Tachycardia

ECG features (Fig. 14)
- Rotating QRS axis in 180° along an imaginary axis (twisting point)
- Associated with long QT interval (also called Torsades de pointes)—congenital long QT syndrome, acquired long QT (drugs, hypokalemia, hypomagnesemia)
- With normal QT interval—coronary ischemia, catecholaminergic VT.

Management:
- Usually associated with hemodynamic compromise—immediate defibrillation
- Torsades de pointes—IV magnesium, beta-blockers, overdrive pacing
- With normal QT—IV beta-blockers, amiodarone, flecainide

Table 3: Antiarrhythmic drugs—Vaughan-Williams classification*.

Class I: Membrane stabilizing agents (sodium channel blockers)
• Block sodium channel and prolong action potential, e.g. quinidine, procainamide • Block sodium channel and shorten action potential, e.g. lidocaine, mexiletine • Block sodium channel and no effect on action potential, e.g. flecainide, propafenone
Class II: Beta adrenoceptor antagonists (β-blockers)
• *Examples*: atenolol, propranolol, esmolol
Class III: Drugs whose main effect is to prolong the action potential
• *Examples*: amiodarone, ibutilide, D-sotalol
Class IV: Slow calcium channel blockers
• *Examples*: verapamil, diltiazem

*This system does not classify adenosine, digoxin or magnesium.

Table 4: Commonly used drugs for ventricular tachycardias.

Drug	*Route*	*Dose*	*Adverse Effects*
Amiodarone	IV	15 mg/min for 10 min, 1 mg/min for 6 h, 0.5 mg/min for next 18 h	QT prolongation and Torsade de pointes, hypotension, bradycardia, tremor, pulmonary fibrosis, hypothyroidism or hyperthyroidism (on long-term therapy)
Procainamide	IV	15 mg/kg over 60 min, followed by 1–4 mg/min	QT prolongation and Torsade de pointes, hypotension (in LV dysfunction), anorexia, systemic lupus erythematosus (on long-term therapy)
Lidocaine	IV	1–3 mg/kg at 20–50 mg/min, followed by 1–4 mg/min	Dizziness, confusion, delirium, seizure, coma

(IV: Intravenous).

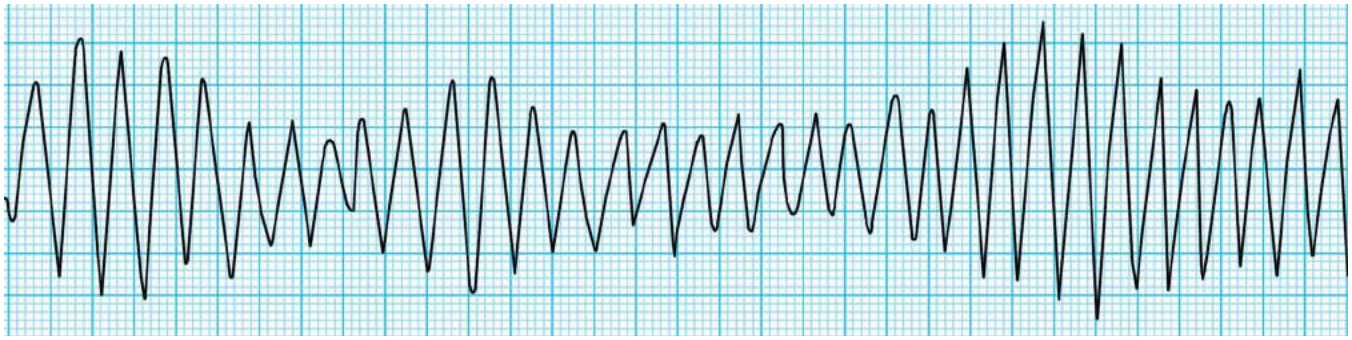


Fig. 14: Polymorphic ventricular tachycardia.

by mansdocs.com

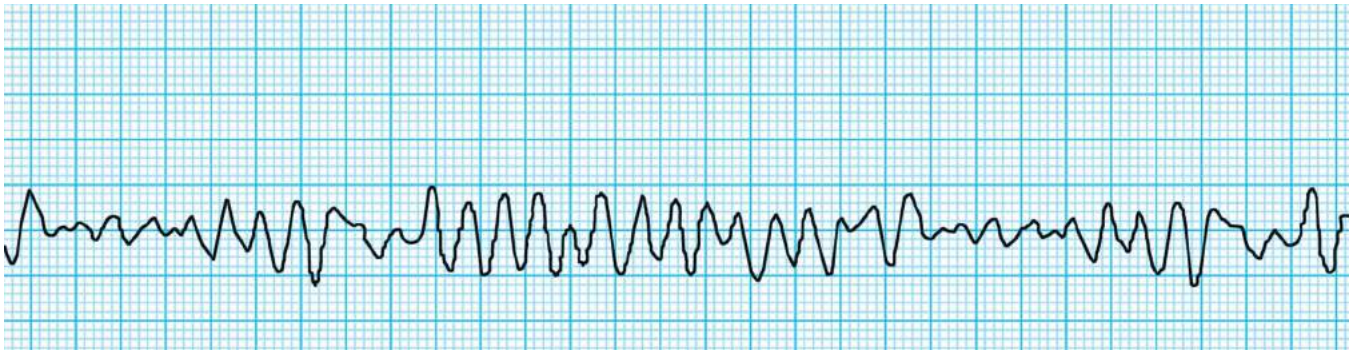


Fig. 15: Ventricular fibrillation.

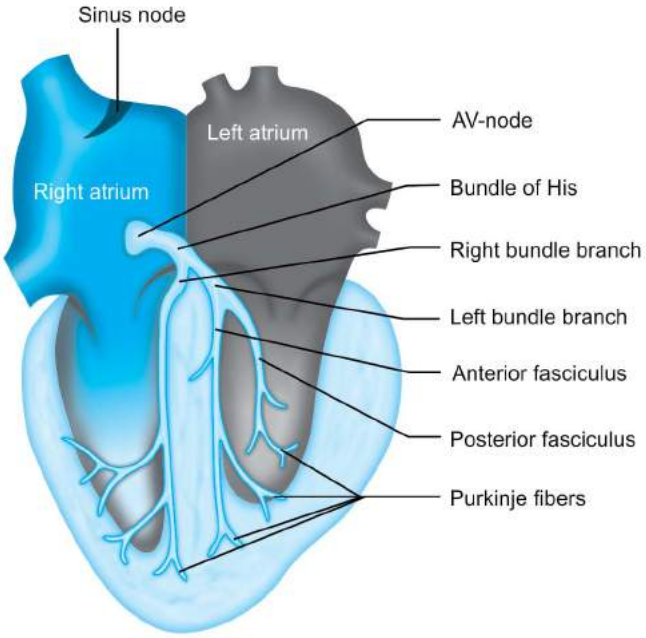


Fig. 16: Cardiac conduction system.

- Treat underlying cause—discontinuation of drugs responsible, correction of electrolytes, treatment of ischemia.

Ventricular Fibrillation

- Irregular waveforms of varying contour, duration and amplitude without identifiable QRS or T waves (Fig. 15)
- Immediate treatment of cardiac arrest.

BRADYARRHYTHMIAS AND CONDUCTION BLOCK

Bradycardia is arbitrarily defined as heart rate of less than 60 beats/min. This may be physiological not requiring any intervention as in an athletic individual or may be pathological. The etiology of bradyarrhythmias could be intrinsic to the conduction system of the heart or may be related to the extrinsic factors like certain drugs. The significance (and treatment) of bradyarrhythmias must be interpreted in the context of clinical scenario and the hemodynamic profile of the patient.

Normal Conduction System

Two types of cells are found in the heart: (1) cells responsible for impulse generation/conduction and (2) cells responsible for contraction (Fig. 16). Normal depolarization and conduction are central to maintaining the chief function of the heart that is generating cardiac output. Under physiological circumstances, depolarization of the myocardium begins in the sinoatrial node (SA node), which is situated at the junction of superior vena cava and the right atrium. The arterial supply of the SA node is from the right coronary artery in 55%, left circumflex artery in 35% and from both in 10% of cases. Initial depolarization of the SA node is not seen in the surface ECG. Impulse is transmitted to the AV node via nonspecialized cells of atria. The depolarization of atria during spread through the atria generates P wave in the ECG.

Normally atria and ventricles are electrically isolated except at the AV node, which is located in the atrial septum at the apex of the triangle of Koch. The conduction through AV node is decremental, allowing the AV node to limit the input to the ventricle in case extremely high atrial impulse generation. AV nodal conduction is responsible for the large part of PR interval. AV node receives its blood supply from the AV nodal artery, which is a branch of right coronary artery in 85% of cases and left circumflex in remaining 15%.

by mansdocs.com

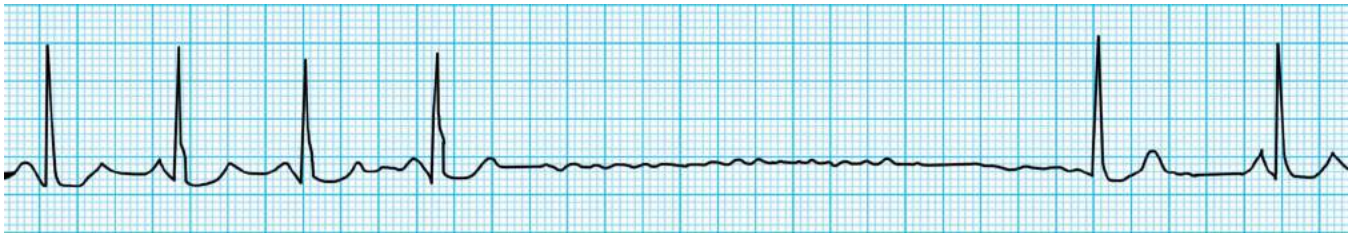


Fig. 17: Sinus node exit block.

After emerging from the AV node, the impulse is conducted via the bundle of His. From there, the impulse travels down the right and left bundle branch (further divided into left anterior fascicle and left posterior fascicle) to the Purkinje network, which causes ventricular contraction. His bundle has a dual blood supply from anterior and posterior septal perforators. Both bundle branches and the fascicles also receive blood supply dually from both right and left coronary system.

Sinus Node Abnormalities

Sinus Bradycardia

Sinus bradycardia is defined as sinus rhythm with a heart rate of less than 60 beats/min. This is seen physiologically in young healthy individuals, athletes, where the sinus rate increases appropriately with exercise. With normal aging, the intrinsic sinus node discharge rate decreases. Inappropriate sinus bradycardia may be seen in intrinsic structural disorder of the SA node or due to extrinsic causes most commonly drugs like beta-blockers or electrolyte abnormalities like hyperkalemia or metabolic problems like hypothyroidism. Ischemia also increases vagal tone causing sinus bradycardia.

Management: Treatment is that of the underlying cause in case of inappropriate bradycardia. If symptomatic IV atropine may be used, temporary pacemaker is only rarely indicated.

Sinus Arrest

Sinus arrest occurs when pacemaker cells fail to depolarize. It is manifested in the surface ECG as absence of P wave or intermittent failure of P wave to appear causing pause. SA exit block and sinus arrest is difficult to distinguish from one another from the surface ECG (Fig. 17). Pauses of less than 3 seconds may be seen in normal healthy individual (particularly amongst athletes) and should not cause concern, but pause more than 3 seconds requires urgent evaluation.

Table 5: Important causes of atrioventricular node dysfunction.

• Drugs	• Digoxin • Beta-blockers • Nondihydropyridine calcium channel blockers • Class I and III antiarrhythmic medications
• Intrinsic cardiac abnormalities	• Ischemia and infarction • Idiopathic fibrosis of the conduction system, e.g. Lenegre's disease • Calcific valvular heart disease • Cardiomyopathies
• Metabolic	• Hyperkalemia • Hypomagnesemia
• Other causes	• Infiltrative diseases, e.g. sarcoidosis • Infections, e.g. Trypanosomiasis or Lyme disease • Rheumatologic disorders, e.g. systemic lupus erythematosus • Trauma • Radiation

Fibrotic degeneration of SA node is common in elderly and is largely responsible for SA node dysfunction requiring permanent pacemaker. It is sometimes manifested when patient is administered certain medications causing SA node exit block like beta-blockers. Certain drugs (beta-blockers, nondihydropyridine calcium channel blockers), toxins (organophosphate insecticides), electrolyte abnormality (hyperkalemia) are other important causes of sinus arrest.

Management: Symptomatic sinus arrest or exit block is treated in the ICU with IV atropine or isoproterenol infusion as a bridge to permanent pacemaker treatment. If the patient fails to respond with medical therapy, temporary pacing is indicated.

Atrioventricular Block (Table 5)

First Degree AV Block

Delay AV conduction is manifested in the ECG as prolonged PR interval more than 200 ms (Fig. 18). It rarely causes symptom and seldom requires further evaluation. Treatment is that of underlying etiology if necessary.

by mansdocs.com



Fig. 18: First-degree atrioventricular block.



Fig. 19: Mobitz type 1 atrioventricular block.



Fig. 20: Mobitz type 2 atrioventricular block.

Second-degree Mobitz Type 1 AV Block (Wenckebach's Phenomenon)

Mobitz type 1 AV block is characterized by progressive lengthening of successive PR interval, culminating in a dropped beat. As the PR interval lengthens, RR interval becomes shorter. QRS complexes are typically grouped in two, three or four (Fig. 19).

This rhythm may be physiological and often found during sleep in athletic young man with high vagal tone. Otherwise also it is a stable rhythm, having a better prognosis than Mobitz type 2 AV block. Treatment, if necessary, is that of underlying etiology.

Second Degree Mobitz Type 2 AV Block

Mobitz type 2 AV block is characterized by intermittent failure of P wave conduction with a constant PR interval. QRS complexes are often wide (Fig. 20). It is always pathological, caused by disease of His-Purkinje system, and carries a risk of asystole. This rhythm often results from anterior wall myocardial infarction.

Management: Treat the underlying etiology. Atropine/isoproterenol/temporary pacing for acute symptomatic patients is recommended. Most patients eventually require permanent pacing.

by mansdocs.com

Third Degree AV Block (Complete Heart Block)

Complete AV block is characterized by complete failure of AV conduction resulting in AV dissociation. Clinically intermittent cannon A-wave may be seen in the jugular venous pulse. Ventricular activity maintained by escape rhythm arising either from the AV node or bundle of His manifested as narrow QRS complex or from the distal Purkinje tissue manifested as broad QRS complex with ventricular rate of less than 40 beats/min (Fig. 21). Infranodal escape rhythm tends to be less reliable and needs urgent intervention.

Nodal complete heart block (CHB) occurs frequently in inferior wall myocardial infarction and is usually transient. CHB, associated with anterior wall myocardial infarction, is usually infranodal and is often irreversible.

Management: Temporary pacing is frequently required in the treatment of CHB and often these patients require permanent pacing. The need for pacing depends upon symptoms and the etiology of CHB.

Atropine

Atropine sulfate is an anticholinergic drug, which increases the sinus rate and SA and AV conduction by vagal inhibition. It is not effective in denervated heart like following cardiac transplantation.

It is used for the initial management of symptomatic bradyarrhythmias and in cardiac arrest due to asystole. Dose is 0.6 mg IV bolus, repeated if necessary up to 3 mg. A dose below 0.3 mg may cause paradoxical decrease in the heart rate.

Adverse effects include dry mouth, thirst, blurred vision, atrial and ventricular premature complexes.

Temporary Pacemakers

Temporary pacing involves delivery of controlled electrical energy via transvenous or transcutaneous route to initiate myocardial depolarization and cardiac contraction.

Transvenous pacing is done by inserting a bipolar electrode via internal jugular, subclavian or femoral vein to the right ventricular apex under fluoroscopic or echocardiographic guidance. Right internal jugular route is preferred for relative ease and lowest rate of complications. The electrode is connected to an external pacemaker with an adjustable energy output and rate. Optimum pacing threshold is considered as less than 1 mA. Since threshold escalates with patient movement and lead dislodgement and also affected by medications, dyselectrolytemia and ischemia, devices are set to discharge at an output of three to five times the threshold. The external pacemaker is nearly always set in a "demand mode" so that it only operates when the intrinsic heart rate of the patient falls below certain preset rate.

The ECG of right ventricular pacing is characterized by regular broad QRS with left bundle branch pattern. A "pacing spike" immediately precedes each complex (Fig. 22).

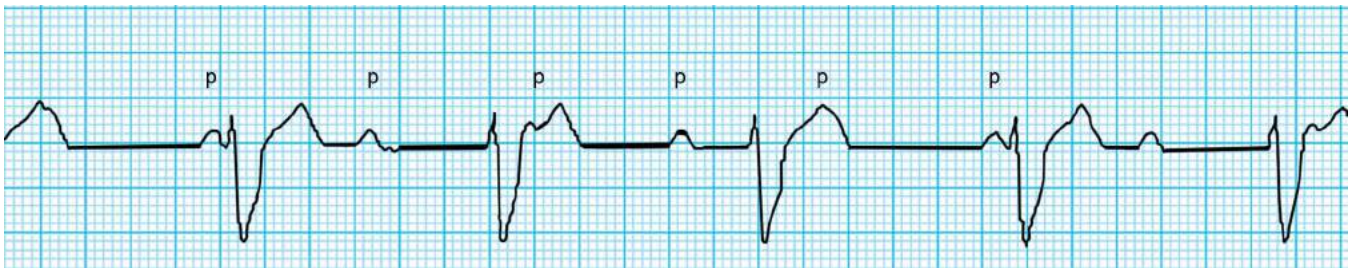


Fig. 21: Complete atrioventricular (AV) block.



Fig. 22: Paced ventricular complexes showing initial "pacing spike".

by mansdocs.com

Complications of transvenous pacing include, that related to central venous catheterization including pneumothorax or infection or myocardial injury including perforation, pericarditis or failure to sense or pace due to lead dislodgement or progressive tissue edema. Complication rates increase with time and temporary transvenous pacemaker should not be in use for more than 7 days.

BIBLIOGRAPHY

1. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61:1935-44.
2. Annane D, Sebille V, Duboc D, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. AJRCCM. 2008;178:20-5.
3. Goldberger ZD, Rho RW, Page RL. Approach to the diagnosis and initial management of the stable adult patient with a wide complex tachycardia. Am J Cardiol. 2008;101:1456-66.
4. Link MS. Evaluation and initial treatment of supraventricular tachycardia. N Engl J Med. 2012;367:1438-48.
5. Mangrum MJ, Dimarco J. The evaluation and management of bradycardia. NEJM. 2000;342:703-9.

by mansdocs.com

CHAPTER

18

Hypertensive Emergency

Yatin Mehta, Mukesh Kumar Gupta

INTRODUCTION

Systemic hypertension is a common medical condition affecting 1 billion population worldwide. It is a risk factor for premature cardiovascular, renal and cerebrovascular disease and is responsible for up to 7 million deaths in a year.

- Hypertension is defined as systolic blood pressure (BP) greater than 140 mm Hg or diastolic BP greater than 90 mm Hg. In patient with known hypertension or otherwise measured on two or more settings, two principle categories of high BP are:
  1. Essential hypertension (primary)
  2. Secondary hypertension
- Essential hypertension has an idiopathic cause. It is the most common cause of hypertension. Essential hypertensive patients have variety of risk factors like family history of hypertension, black rash, dyslipidemia, alcohol intake, obesity and type "A" personality.
- Secondary hypertension accounts for 5–10% of hypertensive patients and is caused by underlying and frequently associated with correctable etiology like primary renal disease, renovascular disease, pheochromocytoma, Cushing syndrome and primary aldosteronism.
- About 1–2% of hypertensive population will present with acute elevation in BP termed hypertensive crisis
- *Hypertensive crisis is further classified into two categories*: (1) hypertensive urgency and (2) hypertensive emergency.

DEFINITION

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in 2003 classified four stages of BP.

1. Normal systolic BP less than 120 mm Hg and diastolic BP less than 80 mm Hg.
2. Prehypertensive systolic BP 121–139 mm Hg and diastolic BP 80–89 mm Hg.
3. Stage I systolic BP 140–159 mm Hg and diastolic BP 90–99 mm Hg.
4. Stage II systolic BP greater than 160 mm Hg and diastolic BP greater than 100 mm Hg.

Although not a category in JNC 7, a systolic BP greater than 180 mm Hg or a diastolic BP greater than 110 mm Hg is termed severe hypertension.

Accelerated Hypertension

Accelerated hypertension is currently recognized as a severely elevated BP with systolic BP greater than 180 mm Hg or diastolic BP greater than 110 mm Hg associated with ocular hemorrhage, exudates and no papilledema (grade III Kimmelstiel-Wilson retinopathy).

Malignant Hypertension

Malignant hypertension is defined as markedly elevated BP and associated with ocular hemorrhage and exudates with papilledema (grade IV Kimmelstiel-Wilson retinopathy). The term malignant hypertension previously relating to encephalopathy or nephropathy is no longer used

by mansdocs.com

and has been removed from national and international BP guidelines and is best referred to as a hypertensive emergency.

Hypertensive Urgency

Hypertensive urgency is defined as a systolic BP greater than 180 mm Hg or a diastolic BP greater than 120 mm Hg in the absence of target end-organ damage. Hypertensive urgency may be associated with chronic stable complication such as stable angina, pervious myocardial infarction, chronic kidney disease and previous transient ischemic attack. Hypertensive urgency may also be associated with inadequately treated BP or noncompliance to the medication.

Hypertensive Emergency

Hypertensive emergency is defined as an elevation of diastolic BP greater than 120 mm Hg with evidence of target end-organ damage including but not limited to cardiac, renal and central nervous systems. Most common hypertensive emergencies are:

- Hypertensive encephalopathy
- Acute stroke—hemorrhagic and ischemic
- Acute coronary syndrome (ACS)
- Acute aortic dissection
- Pulmonary edema with respiratory failure
- Preeclampsia, eclampsia, HELLP syndrome
- Microangiopathic hemolytic anemia—thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

PATHOPHYSIOLOGY

The precise pathophysiology of hypertensive emergency is multifactorial, like mechanical stress and injury, endothelial damage, renin-angiotensin system activation and oxidative stress.

The abrupt release of humoral vasoconstrictors increases the systemic vascular resistance and the BP which generates mechanical stress and causes endothelial damage leading to increased vascular permeability, activation of the coagulation cascade, platelets and deposition of fibrin. This results in ishemia-induced release of aditional vasoactive mediators generating a vicious cycle of organ injury.

The renin-angiotensin system is often activated leading to further vasoconstriction and the production of the inflammatory cytokines such as interleukin-6. Furthermore, NADPH oxidase activity is increased and generates reactive oxygen species. The volume depletion that results from natriuresis further stimulates the release of vasoconstrictor substance from kidney. These collective mechanisms can culminate in end-organ hypoperfusion, ischemia and dysfunction that manifest as a hypertensive emergency.

DIAGNOSIS OF HYPERTENSIVE EMERGENCY

Medical History

Hypertensive emergency usually occurs in individuals with a history of essential hypertension; it is also seen in individuals with secondary hypertension and in individuals with no history of hypertension, preeclampsia, pheochromocytoma and acute glomerulonephritis.

- A focused medical history that includes use of any prescribed or over the counter medication should be obtained. If the patient is a known hypertensive, it is important to know the duration of hypertension, antihypertensive medication that he or she is taking including compliance to medication and drug dosing, as well as the last antihypertensive dose that the patient has taken, before initiating treatment. Inquiring into the use of recreational drugs, such as amphetamines, cocaine, phencyclidine or monoamine oxidase inhibitors, is also necessary.

Physical Examination

The BP is measured in both arms and also with the patient lying and in standing position using an appropriate BP cuff is particularly important because the use of a cuff too small for the arm has been shown to artifactually give elevated BP reading in obese patients.

The physical examination should attempt to identify evidence of end-organ damage by assessing pulse in all extremities, auscultating the lungs for evidence of pulmonary edema, the heart for murmurs or gallop, the renal artery for bruits and performing a focused neurology and fundoscopic examination. Headache and altered level of consciousness are the usual manifestations of hypertensive encephalopathy. Focal neurological findings, especially lateralizing signs, are uncommon in hypertensive encephalopathy, being more suggestive of cerebrovascular accident. Subarachnoid hemorrha should be considered in patients with a sudden onset of severe

by mansdocs.com

headache. Ocular examination may show evidence of advanced retinopathy with arteriolar changes, exudates, hemorrhage or papilledema assessing in the identification of hypertensive encephalopathy. Cardiac evaluation should identify ongoing myocardial infarction with the focus on clarifying any atypical symptoms such as dyspnea, cough or fatigue that may be overlooked. Examination of abdomen should be for enlarged kidneys as well as for evidence of aortic aneurysm.

Laboratory Evaluation

Initial laboratory evaluation should include complete blood count with a peripheral smear to identify schistocyte. Blood sugar to rule out hypoglycemia and kidney function test, including blood urea nitrogen, serum creatinine sodium, potassium, chloride and bicarbonate, prothrombin time, activated partial thrombin time and international normalization ratio, urine analysis for proteinuria, hematuria as well as any cast should be performed. A chest radiograph for those who presents with chest pain or a shortness of breath would be indicative of pulmonary edema or a widened mediastinum. Electrocardiogram to rule out ACS and left ventricular (LV) hypertrophy; two-dimensional (2D) echocardiography to rule out structural heart disease, regional wall motion abnormality, diastolic and systolic dysfunction of ventricles; ultrasonography of kidney, ureter and bladder region to rule out kidney pathology; and renal Doppler to rule out renovascular cause of hypertension; computed tomography scan and magnetic resonance imaging of brain, if stroke and hypertensive encephalopathy suspected, should be done. If the clinical picture is consistent with aortic dissection (chest pain, unequal pulses, widened mediastinum), a contrast computed tomography aortography or magnetic resonance imaging of chest should be obtained promptly to rule out aortic dissection in intubated unstable patients. Transesophageal echocardiography (TEE) can quickly confirm the diagnosis. Serum cortisol, adrenocorticotropic hormone stimulation test should be done for suspected Cushing syndrome. A 24-hour urinary vanillylmandelic acid or serum metanephrine level for suspected pheochromocytoma is done. Urine and serum toxicology screen and pregnancy test when indicated are also done.

TREATMENT OF HYPERTENSIVE EMERGENCY

- Patients with hypertensive emergency are best treated parenterally with antihypertensive drugs in intensive care unit (ICU) monitored by arterial line cannulation or automated BP cuff measurement.
- In most but not all settings, BP can be reduced acutely by 20–25% within minutes to hours. After the patient is stabilized at this pressure, the BP may be further decreased 160–170/100–110 mm Hg over the next 2–6 hours. If the patient is clinically stable, the BP then may be decreased toward a normal BP over 24–48 hours. Once there is a stable BP with intravenous agents and organ damage is ceased, oral therapy can be initiated as the intravenous agents are slowly titrated down.
- Rapid correction of severely elevated BP below autoregulatory range of the vascular bed can result in marked reduction in perfusion causing ischemia and infarction. Therefore, although the BP must be reduced in patients, it must be lowered in a controlled fashion to prevent this impaired autoregulatory hypoperfusion problem.
- Clinical setting where additional consideration and alternative approach to reduced BP should be considered include (1) ischemic stroke where immediate reduction of BP is usually not indicated except when the systolic BP is over 220 mm Hg and diastolic BP is over 120 mm Hg or the patient requires thrombolytic therapy, (2) acute aortic dissection where a rapid BP reduction in 15–30 minutes to a systolic BP is under 100 mm Hg is clinically warranted if the patient tolerates and (3) in previously normotensive subjects with abrupt increase in BP.
- More rapid correction in BP is also recommended in patient with ACS or heart failure with pulmonary edema. Exception to rapid BP reduction may include older patients with carotid stenosis, as they are particularly susceptible to central nervous system hypoperfusion.

PHARMACOLOGIC AGENTS FOR TREATMENT OF HYPERTENSIVE EMERGENCY

Intravenous antihypertensive drugs fall into the broad categories:

- Arterial vasodilators—hydralazine, fenoldopam, nicardipine, clevidipine and enalaprilat
- Mixed venous and arterial vasodilators—sodium nitroprusside (SNP)
- Venous vasodilator—nitroglycerin
- Negative inotropic/chronotropic agent with vasodilators properties, e.g. labetalol, and without vasodilator properties, e.g. esmolol

by mansdocs.com

- Alpha-adrenergic receptor blockers for increased sympathetic activity—phentolamine.

Hydralazine

Hydralazine is a direct arteriolar vasodilator with little or no effect on venous circulation and often causes reflex sympathetic stimulation. Hydralazine should be used with caution in patients with coronary artery disease or aortic dissection unless beta-blocking agents used concomitantly. Hydralazine has been the drug of choice for treatment of preeclampsia or eclampsia as it has limited crossing of the uteroplacental circulation.

Dose: 10 mg every 20–30 minutes, maximum dose 20 mg.

Onset of action: 10–20 minutes.

Duration of action: 2–4 hours.

Contraindication and side effects: Ongoing coronary ischemia, aortic dissection and increased intracranial pressure.

Nicardipine

Nicardipine is a second generation dihydropyridine derivative calcium channel blocker with high vascular selectivity and strong cerebral and coronary vasodilator activity. Nicardipine has been shown to reduce both myocardial and cerebral ischemia and increased both stroke volume and coronary blood flow with a favorable effect on myocardial oxygen balance. It is particularly useful in setting of postoperative hypertensive crisis and neurological condition.

Dose: 5 mg/h, increased at 2.5 mg/h every 5 minutes to maximum of 15 mg/h intravenous infusion.

Onset of action: 5–15 minutes.

Duration of action: 4–6 hours.

Contraindication and side effects: Contraindicated in acute heart failure and coronary ischemia. Side effects are headache, dizziness, flushing, nausea, edema and tachycardia.

Fenoldopam

Fenoldopam is unique among the parenteral BP agents as it mediates peripheral vasodilator by acting on peripheral dopamine-1 receptors. Interestingly, it has the distinct advantage of mediating renal arterial vasodilators by activating dopamine receptors on proximal and distal tubules, and it inhibits sodium reabsorption, thereby promoting natriuresis and diuresis. It is quickly and extensively metabolized by conjugation in the liver without participation of the P450 cytochrome complex.

Dose: Initial dose 0.1 μg/kg/min, 0.05–0.1 μg/kg/min increment every 15 minutes to maximum 1.6 μg/kg/min.

Onset of action: 5–15 minutes.

Duration of action: 30–60 minutes.

Contraindication and side effects: Contraindicated in glaucoma and allergy to sulfites. Side effects are nausea, headache and flushing.

Clevidipine

Clevidipine is third generation dihydropyridine calcium channel blocker that has been developed for use in clinical setting in which tight BP control is crucial. Clevidipine is an ultrashort-acting selective arteriolar vasodilator. It acts by selectively inhibiting the influx of extracellular calcium through the L-type channel, relaxing smooth muscle of small arteries and reducing peripheral vascular resistance. It is rapidly metabolized by red blood cell (RBC) esterases thus its metabolism is not affected by renal or hepatic function. Clevidipine reduces BP by direct and selective effect on arterioles, thereby reducing afterload without affecting cardiac filling pressures or causing reflex tachycardia. Stroke volume and cardiac output usually increase. This drug is not available in India.

Dose: 1–21 mg/h, double rate every 90 second until close to goal then increase rate 5–10 minutes.

Onset of action: 2–4 minutes.

Duration of action: 5–15 minutes.

Contraindication and side effects: Contraindicated in atrial fibrillation and in soy allergy. Side effects are reflex tachycardia.

Enalaprilat

This is a short-acting intravenous angiotensin-converting enzyme (ACE) inhibitor that lowers BP abruptly. It is not widely used in hypertensive emergencies, as it can precipitate hypotension, particularly in volume-depleted patient.

Dose: 1.25–5 mg every 6th hour.

Onset of action: 15–20 minutes.

Duration of action: 12–24 hours.

Contraindication and side effects: Contraindicated in pregnancy and side effects are potential hypotension in high renin states, headache and dizziness.

by mansdocs.com

Sodium Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload. It decreases cerebral blood flow while increasing intracranial pressure effects that are particularly disadvantageous in patient with hypertensive encephalopathy or after cerebrovascular accident. SNP contain 44% cyanide by weight. Cyanide is released nonenzymatically from nitroprusside, the amount generated being dependent on the dose of SNP administered. Cyanide is metabolized in the liver to thiocyanate. Thiosulfate is required for this reaction. Thiocyanate is 100 times less toxic than cyanide. The thiocyanate generated is exerted largely through the kidneys. Cyanide removal therefore requires adequate liver function, adequate renal function and adequate bioavailability of thiosulfate. SNP may therefore cause cytotoxicity due to the release of cyanide with interference of cellular respiration. Cyanide toxicity has been documented to result in "unexplained cardiac arrest", coma, encephalopathy, convulsions and irreversible focal neurologic abnormalities. The current methods of monitoring for cyanide toxicity are insensitive. Metabolic acidosis is usually a preterminal event. In addition, a rise in serum thiocyanate levels is a late event and not directly related to cyanide toxicity. RBC cyanide concentrations (although not widely available) may be a more reliable method of monitoring for cyanide toxicity. An RBC cyanide concentration of 40 nmol/mL results in detectable metabolic changes. Levels 200 nmol/mL are associated with severe clinical symptoms, and levels 400 nmol/mL are considered lethal. Data suggest that SNP infusion rates 4 μg/kg/min, for as little as 2–3 hour may lead to cyanide levels in the toxic range. The recommended doses of nitroprusside of up to 10 μg/kg/min results in cyanide formation at a far greater rate than human beings can detoxify. SNP has also been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation. Considering the potential for severe toxicity with nitroprusside, this drug should only be used when other intravenous antihypertensive agents are not available and then only in specific clinical circumstances and in patients with normal renal and hepatic function. The duration of treatment should be as short as possible. Direct arterial pressure monitoring is necessary due to the potency and rapidity of action of SNP.

Dose: 0.5 μg/kg/min, increase to maximum 4 μg/kg/min to avoid toxicity.

Onset of action: Immediate.

Duration of action: 1–2 minutes.

Contraindication and side effects: Contraindicated in renal, hepatic failure and coronary artery disease. Side effects are thiocyanate and cyanide toxicity, headache, nausea, vomiting, muscle spasm.

Nitroglycerin

Nitroglycerin is a potent venodilator but ineffective arteriolar vasodilator. It reduces BP by decreasing preload and cardiac output. It is an effective drug for patient with severe hypotension and symptomatic ACS, pulmonary edema and in postcoronary artery bypass surgery.

Dose: 5 μg/min, titrated by 5 μg/min every 5–10 minutes to maximum of 100 μg/min intravenous continuous infusion.

Onset of action: 2–5 minutes.

Duration of action: 5–10 minutes.

Contraindication and side effects: Contraindicated in glaucoma, raised intracranial pressure and right ventricular myocardial infarction. Side effects are headache, reflex tachycardia and tachyphylaxis.

Labetalol

Labetalol is a combined selective alpha-1 blocker and nonselective beta-adrenergic receptor blocker with an alpha-to-beta-blocking ratio of 1:7. It is metabolized by liver to form an inactive glucuronide conjugate. It reduces afterload without reducing cerebral, coronary and renal blood flow. It is used in stroke and pregnancy.

Dose: 20 mg initial bolus, 20–80 mg repeated boluses or start infusion 1–2 mg/min with maximum dose 300 mg in 24 hours.

Onset of action: 2–5 minutes.

Duration of action: 3–6 hours.

Contraindication and side effects: Contraindicated in asthma, chronic obstructive pulmonary disease, bradycardia, heart block or heart failure. Side effects are hypotension, dizziness, nausea, vomiting, paresthesia and bronchospasm.

Esmolol

Esmolol is a cardioselective beta-adrenergic blocking agent. Its short half-life of approximate 4 minutes because

by mansdocs.com

of rapid hydrolysis by red blood esterase and this is not dependent on renal or hepatic function for metabolism. The pharmacokinetics and pharmacodynamic properties make esmolol an ideal agent for use in critically ill patients with supraventricular arrhythmia, patient with postoperative hypertension and patient with hypertensive emergency.

Dose: 500 μg/kg loading dose over 1 minute infusion at 25–50 μg/kg/min increased by 25 μg/kg/min every 10–20 minutes to maximum of 300 μg/kg/min.

Onset of action: Immediate.

Duration of action: 1–2 minutes.

Contraindication and side effects: Contraindicated in acute heart failure, bronchoconstrictive disease and heart block. Side effects are nausea, flushing, first-degree heart block and infusion site pain.

Phentolamine

Phentolamine is a pure alpha-adrenergic antagonist utilized for the management of catecholamine-induced hypertensive emergencies. Once initial catecholamine-induced hypertension is under control then oral phenoxybenzamine a long-acting alpha-adrenergic antagonist should be administrated.

Dose: 1–5 mg boluses, maximum 15 mg.

Onset of action: Immediate.

Duration of action: 15 minutes.

Contraindication and side effects: Side effects are flushing tachycardia, dizziness, nausea and vomiting.

SPECIAL CONDITIONS

Cerebrovascular Accident

Stroke is the number one cause of permanent disability in adults. Most patients who present with acute ischemic or hemorrhagic stroke will present with elevated BP likely as an adaptive mechanism to maintain blood flow to the affected area. In these clinical situations, the elevated systemic BP is not a manifestation of hypertensive emergency, but rather a protective physiologic response to maintain cerebral perfusion to the vascular territory affected by ischemia. Because of impaired cerebral autoregulation from chronic hypertension, rapid BP correction can reduce cerebral perfusion and extend the ischemic penumbra to entire arterial territory with catastrophic consequence. The American Stroke Association and the European stroke initiative guidelines recommend withholding antihypertensive therapy for acute ischemic stroke unless there is planned thrombolysis, evidence of concomitant noncerebral acute organ damage, or if the BP is excessively high, arbitrarily chosen as a systolic BP of 220 mm Hg or a diastolic BP of 120 mm Hg based on the upper limit of normal autoregulation. In these patients, the aim is to reduce the pressure by not greater than 10–15% in the first 24 hours. Semplicini and colleagues demonstrated that a high initial BP was associated with a better neurologic outcome following an acute ischemic stroke. In patients receiving thrombolytic therapy, antihypertensive therapy is required for systolic BP of 185 mm Hg or diastolic BP of 110 mm Hg, with a targeted systolic BP of 180 mm Hg and a diastolic BP of 105 mm Hg. The current American Heart Association guidelines recommend the use of labetalol or nicardipine if the systolic BP is 220 mm Hg or the diastolic BP is from 121 mm Hg to 140 mm Hg, and SNP for a diastolic BP of 140 mm Hg. In patients with intracerebral hematomas, there is almost always a rise in intracranial pressure with reflex systemic hypertension. There is no evidence that hypertension provokes further bleeding in patients with intracranial hemorrhage. However, a precipitous fall in systemic BP will compromise cerebral perfusion. The controlled lowering of the BP is currently recommended only when the systolic BP is 200 mm Hg, the diastolic BP is 110 mm Hg, or the mean arterial pressure (MAP) is 130 mm Hg. A study has demonstrated that the rapid decline of BP within the first 24 hours after presentation of an intracranial hemorrhage was associated with increased mortality; the rate of decline in BP was independently associated with increased mortality. Nicardipine has been demonstrated to be an effective agent for the control of BP in patients with intracerebral hemorrhage.

Aortic Dissection

Patients who present to the emergency department with the presumptive diagnosis of aortic dissection should be started on parenteral antihypertensives as soon as possible. The objective of treatment is to lower the pulsatile load and aortic stress by lowering cardiac output and BP with the hope of retarding the propagation of dissection and preventing aortic rupture. A vasodilator alone is not ideal as this can promote reflex tachycardia, increase aortic ejection velocity and promote dissection propagation; therefore, the combination of a beta-adrenergic

by mansdocs.com

antagonist and a vasodilator is the standard approach to treatment. Esmolol is the beta-adrenergic antagonist of choice with metoprolol as a suitable alternative. Although SNP has traditionally been used as the vasodilator of choice, nicardipine or fenoldopam is less toxic, equally effective alternatives. All patients with aortic dissection require cardiovascular surgical consultation to determine if surgical management is necessary. Unless significant medical comorbidities are present, surgery is indicated for all patients with ascending aorta type A dissection. Patients with type B dissections and distal aortic dissections can be managed with aggressive BP control as outcomes have been shown to be the same with either medical or surgical treatment unless complications such as leak, rupture or impaired flow to vital organs supervene. Target BP goal is systolic BP between 100 mm Hg and 120 mm Hg.

Preeclampsia and Eclampsia

The presentation of a patient with pregnancy-induced hypertension (PIH) may range from a mild to a life-threatening disease process. Most preeclamptic patients are vasoconstricted and hemoconcentrated. Initial therapy of preeclampsia includes volume expansion, magnesium sulfate ($MgSO_4$) for seizure prophylaxis and BP control. Delivery is the definitive treatment for preeclampsia and eclampsia. $MgSO_4$ is usually given as a loading dose of 4–6 g in 100 cc D5 1/4 NS over 15–20 minutes followed by a constant infusion of 1–2 g of $MgSO_4$ per hour depending on urine output and deep tendon reflexes, which are checked on an hourly basis. The next step in the management of preeclampsia is to reduce the BP to a safe range being avoiding significant hypotension. The objective of treating severe hypertension is to prevent intracerebral hemorrhage and cardiac failure without compromising cerebral perfusion or jeopardizing uteroplacental blood flow, which is already reduced in many women with eclampsia. Most authorities and the current guidelines from the American College of Obstetricians and Gynecologists recommend keeping the systolic BP between 140 mm Hg and 160 mm Hg and the diastolic BP between 90 mm Hg and 105 mm Hg. This recommendation is supported by a recent study, which demonstrated that a systolic BP greater than 160 mm Hg was the most important factor associated with a cerebrovascular accident in patients with severe preeclampsia and eclampsia. This would suggest that a systolic BP between 155 mm Hg and 160 mm Hg should be the primary trigger to initiate antihypertensive therapy in a patient with severe preeclampsia or eclampsia. Hydralazine has been recommended as the drug of choice to treat severe preeclampsia and eclampsia since the early 1970s. However, hydralazine has a number of properties that make it unsuitable for this indication. Its side effects (such as headache, nausea and vomiting) are common and mimic symptoms of deteriorating preeclampsia. Most importantly, however, it has a delayed onset of action, an unpredictable hypotensive effect and a prolonged duration of action. These properties may result in a precipitous hypotensive overshoot compromising both maternal cerebral blood flow and uteroplacental blood flow. Indeed, in a meta-analysis published by Magee et al., hydralazine was associated with an increased risk of maternal hypotension, which was associated with an excess of cesarean sections, placental abruptions and low Apgar score. Based on the available data, we suggest that hydralazine should not be used as first-line treatment of severe hypertension in pregnancy. Similarly, sublingual or oral nifedipine should be avoided in this setting. Our preference is intravenous labetalol, which is easier to titrate and has a more predictable dose response than hydralazine. It is safe and effective in hypertensive pregnant patients. SNP and ACE inhibitors are contraindicated in pregnant patients.

Sympathetic Crisis

The most commonly encountered sympathetic crises revolve around the recreational use of sympathomimetic drugs such as cocaine, amphetamine or phencyclidine. Rarely, these crises may be seen with pheochromocytoma, a patient taking a monoamine oxidase inhibitor who ingests tyramine-containing food, or patients who abruptly stop antihypertensive medications such as clonidine or beta-adrenergic antagonists. In the clinical situations characterized by sympathetic overstimulation, beta-adrenergic antagonists should be avoided to prevent vascular beta-receptor antagonism resulting in unopposed alpha-adrenergic activity and potential increase in BP. In fact, in cocaine-induced hypertensive emergency, the use of beta-adrenergic blockade can increase coronary vasoconstriction, fail to control heart rate, increase BP and decrease survival. Interestingly, although labetalol is traditionally considered as the ideal agent because of its alpha- and beta-adrenergic antagonism, experimental studies do not support its use in this clinical setting. BP control is best achieved with nicardipine, fenoldopam or verapamil in combination with a benzodiazepine. Phentolamine is an alternative agent.

by mansdocs.com

Myocardial Ischemia

Elevated systemic vascular resistance increases LV myocardial wall tension and oxygen demand. In markedly elevated BP such as in hypertensive emergencies, myocardial perfusion may not be adequately maintained the increased myocardial oxygen demand, which can lead to myocardial ischemia and even infarction. Patients with long-standing hypertension may also have LV hypertrophy, by itself also increases myocardial oxygen demand. This increased LV mass can also cause some degree of coronary artery compression, leading to decreased luminal blood flow. Preferred agents in treating patients with hypertensive emergencies with evidence of ischemia include nitrates that can lower LV preload and improve coronary blood flow as well as beta-blockers that can reduce heart rate, decrease afterload and improve diastolic coronary perfusion. Hydralazine should be avoided, as it can induce a reflex tachycardia and increase cardiac work.

Acute Heart Failure

Acute heart failure presenting as acute pulmonary edema in a hypertensive crisis occurs with an incidence of 36%, making it the second most common sign of end-organ damage. Heart failure can occur in a hypertensive crisis, but it can also be a risk factor for the development of hypertensive crisis. It was initially thought that transient systolic dysfunction causes pulmonary edema in patients with hypertensive crisis, but this theory has been challenged. Gandhi and colleagues used transthoracic echocardiography to evaluate LV ejection fraction during acute episodes of hypertensive pulmonary edema and found that the LV ejection fraction was unchanged during the episodes as well as after treatment. However, they did observe segmental wall motion abnormalities after treatment. The investigators concluded that the cause of acute heart failure in patients with hypertensive crisis may be due to diastolic dysfunction secondary to ischemia. SNP is thought to be the best agent for acute pulmonary edema precipitated by a hypertensive crisis. SNP decreases both preload and afterload. It has a rapid onset of action and a short half-life. Cyanide toxicity is extremely rare. Thiocyanate toxicity is also uncommon and occurs only with high doses of nitroprusside in patients with renal insufficiency. ACE inhibitors, such as enalapril, can be used to reduce afterload and hence improve cardiac output. A new third-generation dihydropyridine calcium channel blocker, clevidipine, was shown in a small study to be effective in reducing BP without adverse events. Loop diuretics such as furosemide are often used in combination with antihypertensive therapy to induce diuresis in hypertensive pulmonary edema.

Acute Postoperative Hypertension

Acute postoperative hypertension has been defined as a significant elevation in BP during the immediate postoperative period that may lead to serious neurologic, cardiovascular or surgical-site complications and requires urgent management. Despite the widespread and long-standing recognition of acute postoperative hypertension, there is no agreement in the literature on a more precise quantitative definition. Acute postoperative hypertension has an early onset, being observed within 2 hours after surgery in most cases, and is typically of short duration, with most patients requiring treatment for up to 6 hours. Complications of acute postoperative hypertension may include hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmia, congestive cardiac failure with pulmonary edema, failure of vascular anastomoses and bleeding at the surgical site. Although acute postoperative hypertension may occur following any major surgery, it is most commonly associated with cardiothoracic, vascular, head and neck, and neurosurgical procedures. The pathophysiologic mechanism underlying acute postoperative hypertension is uncertain and may vary with the surgical procedure and other factors. However, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in these patients. The primary hemodynamic alteration observed in acute postoperative hypertension is an increase in afterload with an increase in systolic BP and diastolic BP with or without tachycardia. There is no consensus concerning the treatment threshold for the management of noncardiac surgery patients with acute postoperative hypertension. Treatment is frequently a bedside decision by the anesthesiologist or surgeon that takes into consideration the baseline BP, concomitant disease and the perceived risk of complications. In contrast, in cardiac surgery patients, treatment is recommended for a BP is 140/90 mm Hg or a MAP of at least 105 mm Hg. Pain and anxiety are common contributors to BP elevations and should be treated before administration of antihypertensive therapy. Other potentially reversible causes of acute postoperative hypertension include hypothermia

by mansdocs.com

with shivering, hypoxemia, hypercarbia and bladder distension. Short-term administration of a short-acting intravenous agent is recommended when there is no identifiable treatable cause of hypertension. Labetalol, esmolol, nicardipine and clevidipine have proven effective in the management of acute postoperative hypertension.

CONCLUSION

Hypertensive emergency represents a serious medical condition with the potential for permanent end-organ damage, and significant morbidity and mortality. Recognition of elevated BP with evidence of end-organ damage should prompt initiation of timely and appropriate parenteral antihypertensive regimens to prevent ongoing end-organ damage. With the development of pharmacologic agents in the last decade, the traditional agent, nitroprusside, should be utilized significantly less given that the other agents, such as esmolol, nicardipine and fenoldopam, are now available and are equally effective with fewer adverse effects. It should be stressed that the use of oral or sublingual nifedipine should be avoided to prevent increased mortality.

BIBLIOGRAPHY

1. Aggarwal M, Khan IA. Hypertensive crisis: hypertensive emergencies and urgencies. Cardiol Clin. 2006;24(1):135-46.
2. Flanigan JS, Vitberg D. Hypertensive emergency and severe hypertension: what to treat, who to treat, and how to treat. Med Clin North Am. 2006;90(3):439-51.
3. Hebert CJ, Vidt DG. Hypertensive crises. Prim Care. 2008;35(3):475-87.
4. Johnson W, Nguyen ML, Patel R. Hypertension crisis in the emergency department. Cardiol Clin. 2012;30(4):533-43.
5. Marik PE, Rivera R. Hypertensive emergencies: an update. Curr Opin Crit Care. 2011;17(6):569-80.
6. Marik PE, Varon J. Hypertensive crises: challenges and management. Chest. 2007;131(6):1949-62.

by mansdocs.com

CHAPTER

19

Pacing in the ICU Setting

Balbir Singh, Lakshmi N Kottu

The purpose of cardiac pacing is to restore or ensure effective cardiac depolarization. Indications include symptomatic bradyarrhythmias and overdrive pacing for tachyarrhythmias. Pacing for asystole has very minimal success, but has been used for this condition. Several approaches to pacing can be taken, including transcutaneous, transvenous, transthoracic, epicardial, endocardial and esophageal. Transcutaneous and transvenous are the two techniques most commonly used in the emergency department (ED). Transcutaneous pacing is the technique of choice in the ED when time is of the essence. Transcutaneous pacing is generally a temporizing measure that may precede transvenous cardiac pacing.

The transvenous method of endocardial pacing is commonly used and is both safe and effective, and can be performed rapidly in vast majority of patients. However, it should not be performed without a thorough understanding of its indications, contraindications and complications. However, because this procedure is essentially performed in a blind manner, sometimes it will not be successful.

HISTORICAL PERSPECTIVES

The ability of muscle to be artificially depolarized was recognized as early as the 18th century. Initial efforts focused on the transcutaneous approach. In 1951, Callaghan and Bigelow first used the transvenous approach to stimulate asystolic heart in hypothermic dogs.

Furman and Robinson first demonstrated the transvenous endocardial approach in humans in 1958 by treating two patients with complete heart block and Stokes-Adams attacks. Other early clinical studies also demonstrated the utility of transvenous pacing. Fluoroscopic guidance was used for placement of the pacing catheter in all these studies.

In 1965, Kimball and Killip used this technique to insert endocardial pacemakers at the bedside. At this stage, all intracardiac pacing was done asynchronously, which meant that the pacing catheter could cause electrical stimulation during any phase of the cardiac cycle. Asynchronous pacing frequently resulted in the pacemaker firing during the vulnerable period of an intrinsic depolarization; this occasionally caused ventricular tachycardia (VT) or ventricular fibrillation (VF). In 1967, a demand pacemaker generator that sensed intrinsic depolarizations and inhibited the pacemaker for a predetermined period was used successfully by Zuckerman et al.

In 1970, Swan and Ganz introduced the technique of heart catheterization with a flow-directed balloon-tipped catheter. Schnitzler and colleagues successfully used this method for placement of a right ventricular pacemaker in 15 of 17 patients.

INDICATIONS

In general, the indications can be grouped into those that cause either tachycardias or bradycardias. Transcutaneous cardiac pacing (TCP) has become the mainstay of emergency cardiac pacing and is often used while preparing for placement of a transvenous catheter.

by mansdocs.com

Bradycardias

Asystolic Arrest

Transvenous pacing in an asystolic patient has little value and is not recommended. In a study of 13 patients who had suffered cardiac arrest, capture of the myocardium was noted in 4 patients, but there were no survivors. This failure of pacing thus suggests lack of effective pacing is primarily related to the state of the myocardial tissue. Continued effort at chest compressions is far superior to interrupt compressions and try pacing techniques in an asystolic patient.

Sinus Node Dysfunction

Sinus node dysfunction may be manifested as sinus arrest, tachy-brady (sick sinus) syndrome, or sinus bradycardia. Although symptomatic sinus node dysfunction is a common indication for elective permanent pacing, it is seldom cause for emergency pacemaker insertion.

Sinus node dysfunction frequently responds to medical therapy and generally gives enough time for physician to avoid bedside pacing.

Atrioventricular Blocks

Atrioventricular block is the classic indication for pacemaker therapy and can occur both in setting of acute myocardial infarction (AMI) or without it. In patients without AMI, pacing is indicated if the patient is symptomatic with giddiness or Stoke-Adams attacks, or, if not symptomatic, ventricular rate is less than 40 beats/minute.

In patients with AMI, 15–19% progress to heart block with third degree heart block in 6% of patients. Atrioventricular block occurring during anterior wall myocardial infarction is believed to result from diffuse ischemia in the septum and infranodal conduction tissue and thus aggressive management is mandatory.

During inferior wall infarction, blocks are hemodynamically tolerable escape rhythms because of sparing of the bundle branches. A hemodynamically unstable patient who is unresponsive to medical therapy should be paced promptly.

Drug-Induced Bradycardias

Severe bradycardia and heart block often accompany over dose of digitalis preparations, β-adrenergic blockers, and calcium channel blockers; however, medically managing them produces superior outcomes than pacing.

Tachycardias

Hemodynamically compromising tachycardias are usually treated by medical means or electrical cardioversion. Supraventricular dysrhythmias, with the exception of atrial fibrillation, respond well to atrial pacing. By "overdrive" pacing, the atria beat at rates 10–20 beats/minute faster than the underlying rhythm, the rhythm frequently returns to normal sinus. Overdrive pacing is especially useful for arrhythmias with recurrent prolonged QT intervals such as those seen with drug toxicity or torsades de pointes.

Significant dysrhythmias can be caused by excessive therapeutic medication like amiodarone or other class I antiarrhythmic particularly in the setting of electrolyte abnormalities. Common dysrhythmias are polymorphic VT or Torsade de pointes. In our experience, atrial pacing at rates of 90–100 beats/minute helps to suppress these arrhythmias and also maintains hemodynamics in patients who generally also have left ventricular dysfunction.

PROCEDURAL DETAILS

Equipment

Pacing (Pulse) Generator

Many different battery operated pacing generators are available, but in general, they all have the same basic features. Three basic controls, current, sensitivity and rate, on the generator allow the proper functioning of the device. A current control allows the operator to vary the amount of electrical current delivered to the myocardium, usually 0.1–20 mA. Increasing the setting increases the output and improves the likelihood of capture. By increasing the sensitivity, one can convert the unit from a fixed-rate (asynchronous mode) to a demand (synchronous mode) pacemaker. The typical pacing generator has a sensitivity setting that ranges from about 0.5–20 mV. The voltage setting represents the minimum strength of electrical signal that the pacer is able to detect. Decreasing the setting increases the sensitivity and improves the likelihood of sensing myocardial depolarization. In the full-demand mode, the pacemaker senses the underlying ventricular depolarizations, and the unit does not fire as long as the patient's ventricular rate is equal to or faster than the set rate of the pacing generator.

Introducer Sheath

An introducer set or sheath is required for venous access. The introducer set is used to enhance passage of the pacing

by mansdocs.com

catheter through the skin, subcutaneous tissue and vessel wall. Since size 5 or 6 Fr pacing catheters are used for pacing a 6 Fr sheath is quite adequate for the procedure, the introducer sheath allows for smooth passage of the catheter and prevents back flow of blood. The introducer sheath set includes a puncture needle, 0.035 inch or 0.038 inch, guidewire and a sheath.

Pacing Lead

Several sizes and brands of pacing catheters are available. In general, most range from 5 Fr to 6 Fr in size and are approximately 100 cm in length. Pacing catheters differ with respect to their stiffness, electrode configurations, floating characteristics, and other qualities. For emergency pacing, the semi-floating bipolar electrode catheter with a balloon tip can be used effectively.

All pacemaker systems have both a positive (anode) and a negative (cathode) electrode; hence, all stimulation is bipolar. In the typical bipolar catheter used for temporary transvenous pacing, the cathode (stimulating electrode) is at the tip of the pacing catheter. The anode is located 1–2 cm proximal to the tip. When properly positioned, both electrodes will be within the right ventricle or right atrium, so that a field of electrical excitation is set up between the electrodes.

Connecting Cable

This allows connecting the pins of the pacing lead to the generator and allows for bipolar pacing; some generators allow direct connection of the pins of the lead. The connection cable allows for the extra length to permit pacemaker generator to be kept in a secure place.

Procedural Characteristics

The four venous channels that provide easy access to the right ventricle are the brachial, subclavian, femoral and internal jugular vein. The right jugular vein and left subclavian vein provide a more direct route to the right side of the heart since right jugular vein access carries lower risk and is the preferred route for insertion of pacing lead.

All aseptic precautions should be taken. For any invasive procedure the skin should be prepared and draped, the right internal jugular is punctured using standard techniques.

Ultrasound guidance is helpful in obtaining venous access. In patients with indwelling central lines, a wire could be passed to exchange the line for the sheath.

An accurate placement of the lead in right ventricle with the help of an image intensifier is easy, but performing pacing at bedside can pose challenges.

A rough estimate of the length of the lead required inside the body can be made by measuring the distance from the sheath to the 4th intercostal space on left side. At this stage, insert the lead into the sheath and attach the lead to the pacing generator through the connecting cable, set the generator to an output of 10 mA, rate to 80 beats/minute and sensitivity to 3 V, keep inserting the lead while carefully observing the electrocardiogram (ECG) lead on the monitor (lead II and VI are most useful). It is important to recognize the pacing spike, and its relationship to QRS. This is crucial since sometimes only a pacing spike is seen (Figs. 1 and 2) and physician may feel he has achieved pacing, so presence of QRS following the spike or presence of T wave following the spike establish capture (Fig. 3). Another simple way of establishing capture is to observe arterial blood pressure trace following the pacing spike, i.e. each pacing spike should be followed by ejection on the monitor.

Testing Threshold

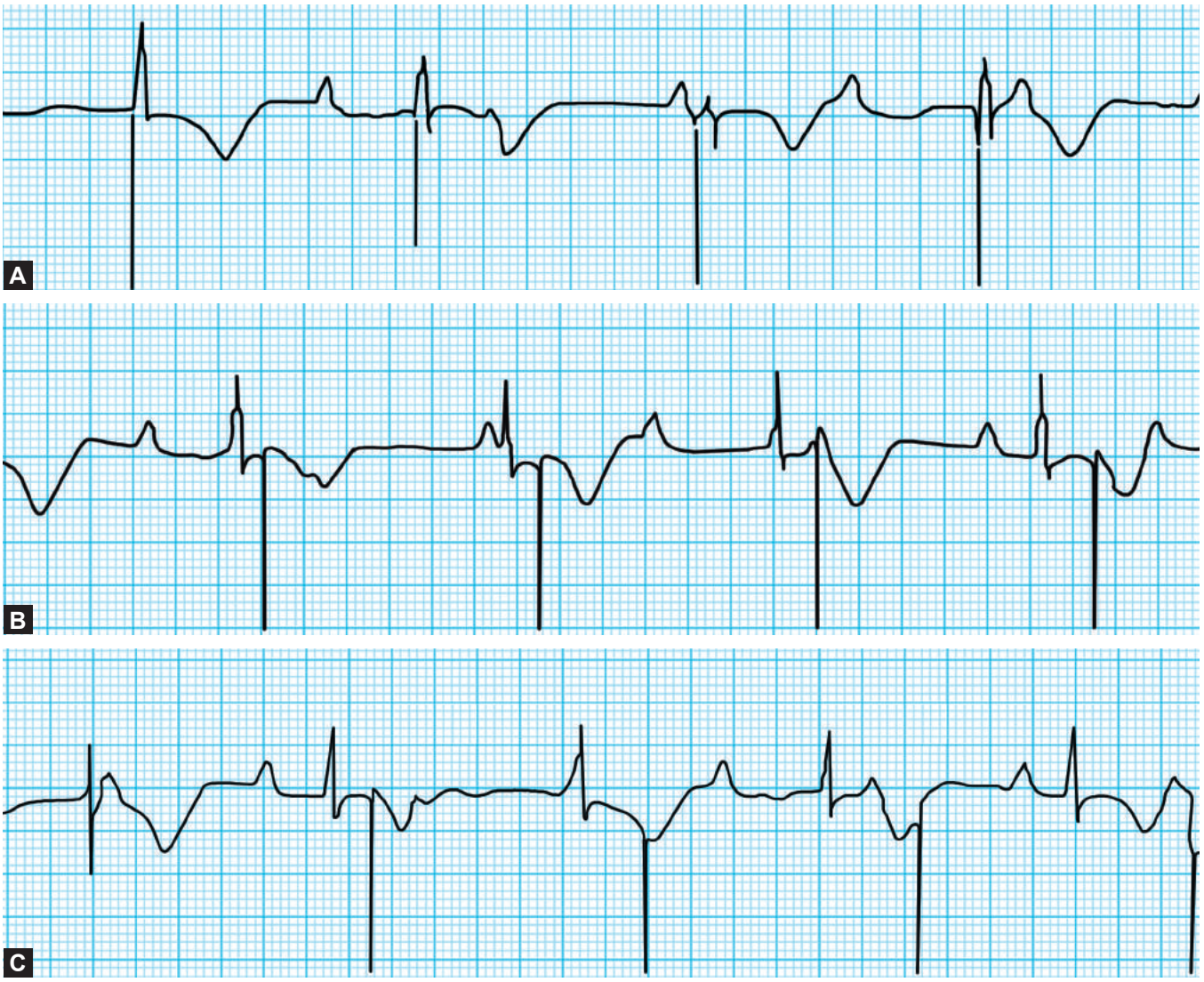
Threshold is the minimum current necessary to obtain pacing capture. Ideally, it is less than 1.0 mA. If the threshold is in this ideal range, good contact with the endocardium can be presumed.

To determine the threshold, set the pacing generator to maximum sensitivity (full-demand mode) at 10 mA output and a rate of approximately 80 beats/minute (or at least 10 beats/minute greater than the patient's intrinsic rate). Reduce the current (output) slowly until capture is lost. This current is the threshold. Carry out this maneuver two or three times to ensure that this value is consistent. Increase the amperage to 2.5 times the threshold to ensure consistency of capture.

Testing Sensitivity

Test the sensing function in patients who have underlying rhythms. Set the rate at about 10 beats/minute lower than the endogenous rhythm, place the pacemaker in asynchronous mode (minimum sensitivity, which is the maximum setting on the sensitivity voltage control), then adjust the sensitivity control to its mid-position or approximately 3 mV. The sensing indicator on the pacing generator should signal each time that a native beat is sensed and should be in synchrony with each QRS complex on the ECG monitor.

by mansdocs.com



Figs. 1A to C: Multiple pacing spikes but none seems to capture; intrinsic QRS complexes noted which are not being sensed indicating failure to pace or sense.

Final Assessment

After the pacemaker's position has been tested for electrical accuracy, it must be secured in place. The introducer sheath hub should be fixed firmly to the skin with suture. The excess pacing catheter length should then be coiled and secured in a sterile manner underneath a large sterile dressing. Take a chest X-ray film and a 12-lead ECG to ensure proper positioning. X-ray film is obtained to ensure that there is no pneumothorax and check the lead position.

A 12-lead ECG tracing should be obtained after placement of the transvenous pacemaker. If the catheter is within the right ventricle, a left bundle branch pattern with left axis deviation should be evident in paced beats (Fig. 3). If a right bundle branch block (RBBB) pattern is noted, coronary sinus placement or left ventricular pacing secondary to septal penetration should be suspected.

COMPLICATIONS

The complications associated with emergency transvenous cardiac pacing are numerous and represent those related to central venous catheterization, those related to right-sided heart catheterization, and the pacing catheter itself.

by mansdocs.com

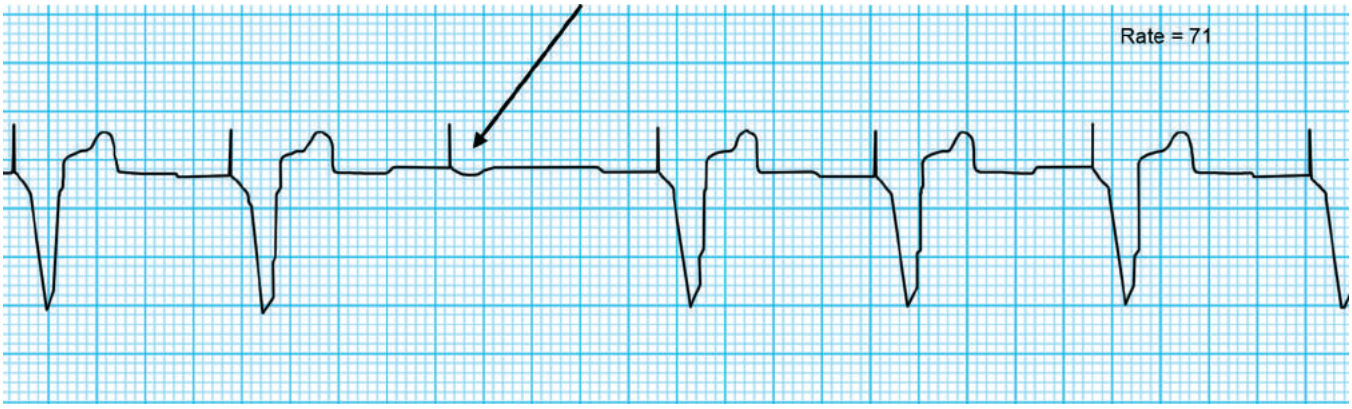


Fig. 2: Complex 3 shows a spike but no QRS complex indicating a failure to capture

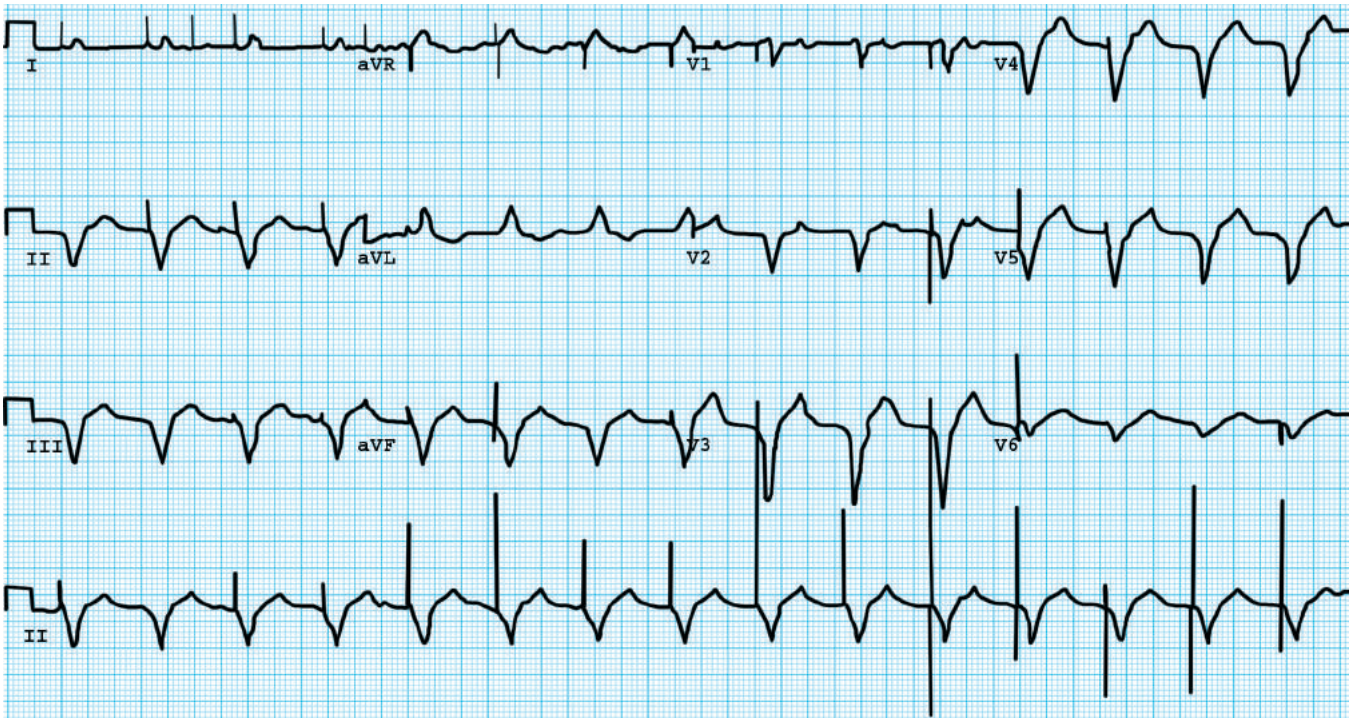


Fig. 3: A 12-lead ECG shows pacing spike followed by QRS complex; note left bundle branch block morphology with left axis deviation indicating pacing near right ventricular apex

Local Site Complications

Inadvertent arterial puncture, venous thrombosis and thrombophlebitis are also potential problems with central venous catheterization. Femoral vein thrombosis, however, appears to be a much more common event associated with femoral vein catheterization. Most patients should get prophylactic low-molecular heparin unless contraindicated.

Pneumothorax is a problem with the various approaches to the veins at the base of the neck. The decision to place a chest tube in patients with this complication depends on the extent of the air leak and the clinical status of the patient.

Complications of Lead Placement

A frequent complication of the pacing catheter is dysrhythmia, with premature ventricular contractions being a common occurrence. Therapy for catheter-induced ectopy during insertion involves repositioning the catheter in the ventricle.

by mansdocs.com

Perforation of the ventricle is a well-described and dreaded complication that can result in loss of capture, hemopericardium and tamponade. Reported symptoms and signs of this problem include chest pain, pericardial friction rub and diaphragmatic or chest wall muscular pacing and hypotension.

Pericardial perforation is suggested radiographically when the pacing catheter is outside or abuts the cardiac silhouette and is not in proper position within the right ventricular cavity. In suspected cases, a two-dimensional echocardiogram usually demonstrates the catheter's extracardiac position. Simply pulling the catheter back and repositioning it in the right ventricle can usually treat uncomplicated perforation.

Lead displacement is pretty common particularly when it is in place for several days, like any invasive time in the ICU; a temporary pacing lead can lead to sepsis either local skin or blood stream infection which may result in thrombus on the lead or bacterial endocarditis.

EMERGENCY TRANSCUTANEOUS PACING

Transcutaneous cardiac pacing (TCP) is a rapid, minimally invasive method of emergency cardiac pacing that may temporarily substitute for transvenous pacing. Electrodes are applied to the skin of the anterior and posterior chest walls, and pacing is initiated with a portable pulse generator. In an emergency setting, this pacing technique is faster and easier to initiate than transvenous pacing.

In 1952, Zoll introduced the first practical means of TCP. Using a ground electrode attached to the skin and a subcutaneous needle electrode over the precordium, he reported successful resuscitation of two patients in ventricular standstill. Refinements in electrode size and pulse characteristics led to the reintroduction of TCP into clinical practice. Electrodes with a larger surface area (80–100 cm^2) decrease the current density at the underlying skin, and therefore decrease pain and the possibility of tissue burns.

Transcutaneous cardiac pacing is the fastest and easiest method of emergency pacing. This technique is useful for initial stabilization of patients in the ED who require emergency pacing while arrangements or decisions about transvenous pacemaker insertion are being made. TCP is also widely used in the prehospital environment, as well as, in the hospital, in the cardiac catheterization laboratory, operating room and intensive care units.

Two sets of patient electrodes are usually required for operation of the device. One set of standard ECG electrodes is used for monitoring. The much larger pacing electrodes deliver electrical impulses for pacing. Newer combined defibrillator-pacemakers can use a single set of electrodes for ECG monitoring, pacing and defibrillation.

The major potential complication of TCP is failure to recognize the presence of underlying treatable VF. This complication is primarily due to the size of the pacing artifact on the ECG screen, a technical problem inherent in systems without appropriate dampening circuitry. Soft tissue discomfort with the potential for injury may still occur with current transcutaneous pacemakers. Most patients are able to tolerate the discomfort, especially after sedation and analgesia. Every intensivist's should be able to identify the indication for emergency pacing in the ICU and should be able to initiate it in the ICU itself either transvenous or TCP till the cardiologist arrives. This may effectively save many lives.

BIBLIOGRAPHY

1. Ayerbea JL, Sabatéa RV, Garcíaa CG, et al. Temporary pacemakers: current use and complications. Rev Esp Cardiol. 2004;57:1045-52.
2. Bessman ES. Emergency cardiac pacing. In: Roberts JR, Hedges JR (Eds). Clinical Procedures in Emergency Medicine, 5th edition. Philadelphia: Elsevier Inc.; 2010.
3. Furman S. The early history of cardiac pacing. Pacing Clin Electrophysiol. 2003;26:2023-32.
4. Harrigan RA, Chan TC, Moonblatt S, et al. Temporary transvenous pacemaker placement in the emergency department. J Emergen Med. 2007;32:105-11.
5. Kimball JT, Killip T. A simple bedside method for transvenous intracardiac pacing. Am Heart J. 1965;70:35-9.
6. Muñoz Bono J, Prieto Palomino MA, Macías Guarasa I, et al. Efficacy and safety of non-permanent transvenous pacemaker implantation in intensive care unit.Med Intensiva. 2011; 35(7):410-6.
7. Noe R, Cockrell W, Moses HW, et al. Transcutaneous pacemaker use in a large hospital. Pacing Clin Electrophysiol. 1986;9:101-4.
8. Resnekov L, Lipp H. Pacemaking and acute myocardial infarction. Prog Cardiovasc Dis. 1972;14:475-99.
9. Rosenberg AS, Grossman JI, Escher DJ, et al. Bedside transvenous cardiac pacing. Am Heart J. 1969;77:697-703.
10. Syverud SA, Dalsey WC, Hedges JR. Transcutaneous and transvenous cardiac pacing for early bradyasystolic cardiac arrest. Ann Emerg Med. 1986;15:121-4.
11. Weiner I. Pacing techniques in the treatment of tachycardias. Ann Intern Med. 1980;93:326-9.
12. Wood MA. Special problems in cardiac pacing. In: Crawford MH, DiMarco JP, Paulus WJ (Eds). Cardiology, 3rd edition. Philadelphia: Elsevier Inc.; 2010.

by mansdocs.com

CHAPTER

20

Pulmonary Embolism

Rajesh Chawla, Manish Bharti

INTRODUCTION

Pulmonary embolism (PE) is one of the most common preventable causes of death with a mortality rate of approaching as high as 30% without treatment. Most deaths are due to recurrent PE within the first few hours of the initial event. Anticoagulation and fibrinolytic therapy decreases the in-hospital mortality rate to as low as 3–8%, making it imperative to initiate early treatment.

The diagnosis of PE is often a diagnostic challenge because of its highly variable clinical presentation. High index of clinical suspicion is essential to make an early diagnosis.

PATHOPHYSIOLOGY

Normal coagulation and fibrinolytic system represent the balance between the thrombogenic stimuli and protective mechanisms. Historically Virchow's triad, which includes venous stasis, activation of blood coagulation and vascular damage, has been stated as the predisposing risk factors for the deep vein thrombosis (DVT) and subsequently venous thromboembolism (VTE). Concurrently there are many protective mechanisms that operate to counteract these thrombogenic factors including the inactivation of activated coagulation factors by circulating inhibitors (e.g. antithrombin III, α2-macroglobulin, α1-antitrypsin and activated protein C). Simultaneously there is ongoing clearance of activated coagulation factors and soluble fibrin/polymer complexes by the reticuloendothelial system and liver; and continuous dissolution of fibrin by fibrinolytic enzymes present in the plasma and endothelial cells, and thereafter digestion of fibrin by leukocytes. The risk of VTE exponentially increases when more than one predisposing factors are present. Activated protein C resistance has been rated as the commonest hereditary abnormality predisposing to VTE. This results from the substitution of glutamine for arginine at residue 506 in the factor V molecule, making factor V resistant to proteolysis by activated protein C. Another inheritable gene mutation designated as factor V Leiden mutation. Patients who are homozygous for the factor V Leiden mutation have a markedly increased risk of thromboembolism and present with clinical thromboembolism at a younger age (median 31 years) than those who are heterozygous (median age 46 years). Factor V Leiden is present in approximately 5% of the normal Caucasian population, 16% of patients with a first episode of DVT, and up to 35% of patients with idiopathic DVT. Prothrombin G20210A is another gene mutation that predisposes to VTE. It is present in approximately 2–3% of apparently healthy individuals and in 7% of those with DVT. An inherited abnormality cannot be detected in up to 40–60% of patients with idiopathic DVT, suggesting that other gene mutations are present and have an etiologic role.

In more than 90% of the cases the PE originates from thrombi in the deep veins of the leg. Popliteal or more proximal deep veins of the leg are the commonest source for clinically important PE. Other less possible sources include the deep pelvic veins, renal veins, inferior vena cava, right ventricle and axillary veins.

by mansdocs.com

The usual incidence of PE accounts for near to 50% in patients with objectively documented proximal vein thrombosis; many of these emboli are asymptomatic. Almost 60% of patients who have angiographically documented PE have detectable DVT of the legs at the time of presentation. The size of the embolus and the individual cardiopulmonary reserve decides the clinical presentation from sometimes merely asymptomatic to the massive cardio-collapse.

CLINICAL FEATURES

Deep vein thrombosis includes a varied presentation which includes the leg pain, tenderness and swelling, a palpable cord, discoloration, venous distention, prominence of the superficial veins and cyanosis. The clinical diagnosis DVT often lacks specificity because none of the symptoms or signs is unique, and each may be heralded by numerous non-thrombotic disorders. It is not unusual to have patients with relatively minor symptoms and signs to have extensive DVT, whereas those with florid leg pain and swelling, having negative results for DVT on objective testing.

Objective testing is therefore considered mandatory to confirm or exclude a diagnosis of DVT. Recurrence of VTE is significantly influenced by the location of the initial DVT, for example, the presence of an ilial femoral vein thrombosis has been shown to have a higher rate of recurrent VTE compared with popliteal vein thrombosis. As discussed above the clinical presentation of PE depends mainly on the size, location and number of emboli, and the individual underlying cardiopulmonary reserve. Clinical manifestations of acute PE is usually quite variable and non-specific that overlap considerably, from transient dyspnea and tachypnea to pulmonary infarction or congestive atelectasis (ischemic pneumonitis or incomplete infarction), which includes pleuritic chest pain, cough, hemoptysis, pleural effusion and pulmonary infiltrates on the chest X-ray. Often subset of population presents with right ventricular failure associated with severe dyspnea and tachypnea.

Cardiovascular collapse associated with severe hypotension, is not uncommon in patients with sub-massive and massive PE. Less common and highly nonspecific clinical features include confusion and coma, pyrexia, wheezing, resistant cardiac failure and unexplained arrhythmia. Small fraction of patients present with recurrent VTE.

Factors contributing to recurrent VTE include length of initial hospitalization, presence of cancer, older age, hospitalization for multiple injuries, and surgery within 3 months. Risk factors for an adverse outcome include factors such as older than age 70, hypotension, congestive heart failure, chronic obstructive pulmonary disease (COPD), cancer, presence of a DVT, and right ventricular hypokinesis on echocardiography (Table 1). Stratification tools such as PE Severity Index (PESI) and measurement of troponin and BNP estimation is considered to be useful in the initial diagnosis and estimating prognosis in patients presenting with PE.

Table 1: Risk factors for pulmonary embolism.

Major risk factors:	
Surgery*	• Major abdominal/pelvic surgery • Hip/Knee replacement • Postoperative intensive care
Obstetrics	• Late pregnancy • Cesarean section • Puerperium
Lower limb problems	• Fracture • Varicose veins
Malignancy	• Abdominal/Pelvic • Advanced/Metastatic
Reduced mobility	• Hospitalization • Institutional care
Miscellaneous	• Previous proven VTE
Minor risk factors (relative risk 2–4):	
Cardiovascular	• Congenital heart disease • Congestive cardiac failure • Hypertension • Superficial venous thrombosis • Indwelling central vein catheter
Oestrogens	• Oral contraceptive • Hormone replacement therapy
Miscellaneous	• COPD • Neurological disability • Occult malignancy • Thrombotic disorders • Long distance sedentary travel • Obesity • Other†

*Where appropriate prophylaxis is used, relative risk is much lower.
†Inflammatory bowel disease, nephrotic syndrome, chronic dialysis, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, Behçet's disease.
(COPD: Chronic obstructive pulmonary disease).

by mansdocs.com

INITIAL RESUSCITATION

When a patient presents with suspected acute PE, the initial focus should be on supporting the cardiorespiratory system. This may require respiratory support, hemodynamic support, and/or empiric anticoagulation.

Respiratory Support

Consider supplemental oxygen to keep the SaO_2 more than 90%. Role of noninvasive ventilation is controversial; however, it is often given in mild-moderate hypoxemia to support work of breathing. Subset of patients presenting with severe hypoxemia or overt respiratory failure should prompt consideration of intubation and mechanical ventilation. Of note, patients with coexistent right ventricular (RV) failure are prone to hypotension following intubation.

Hemodynamic Support

Hemodynamic support should be instituted when a patient presents with hypotension. Hypotension often as a part of massive PE defined as a systolic blood pressure less than 90 mm Hg or a drop in systolic blood pressure of more than or equal to 40 mm Hg from baseline, but the precise thresholds that warrant hemodynamic support depend to some degree upon the patient's baseline blood pressure and whether there is clinical evidence of tissue hypoperfusion (e.g. change in mental status, diminished urine output).

Intravenous Fluid Therapy

Intravenous fluid administration is first-line therapy. Administration of 500–1000 mL of crystalloid as a fluid challenge may significantly increase the cardiac index. Overzealous fluid resuscitation should be avoided as it predisposes to increased right ventricular wall stress which can significantly decrease the ratio of RV oxygen supply to demand. This overall may result in ischemia, deterioration of RV function and further RV failure.

Vasopressor/Ionotropic Support

Early vasopressor/ionotropic therapy should be considered to support the circulation in case of failure of response to fluid challenge/fluid therapy.

Among the ionotropes/vasopressors, combination of dobutamine with noradrenaline seems to be ideal. Dobutamine increases myocardial contractility and causes vasodilation (i.e. decreases afterload), which is ideal for cardiogenic shock. However, the effects of vasodilation can exceed those of increased myocardial contractility and worsen the hypotension, particularly at low doses. Combination with norepinephrine minimizes the vasodilation and the risk of hypotension. As the dose of dobutamine is increased, the effects of the increased myocardial contractility may exceed those of the vasodilation, allowing the norepinephrine to be weaned off and the dobutamine to be used alone.

Detail medical examination and identification of risk factors for the DVT/PE should be simultaneously sought.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis in case of pulmonary embolism is quite extensive. For the patients presenting within dyspnea and tachypnea, differential include atelectasis, pneumonia, pneumothorax, acute pulmonary edema, bronchitis, bronchiolitis and acute bronchial obstruction. For patients having pulmonary infarction exhibited by pleuritic chest pain or hemoptysis, differential include pneumonia, pneumothorax, pericarditis, pulmonary or bronchial neoplasm, bronchiectasis, acute bronchitis, tuberculosis, diaphragmatic inflammation, myositis, muscle strain and rib fracture.

For the clinical presentation of right-sided heart failure, they include myocardial infarction, myocarditis and cardiac tamponade. For cardiovascular collapse, they include myocardial infarction, acute massive hemorrhage, Gram-negative septicemia, cardiac tamponade and spontaneous pneumothorax.

ASSESS CLINICAL PROBABILITY OF PULMONARY EMBOLISM

Various clinical probability scores like revised Geneva scores and Well's score (Tables 2 and 3) have been described which usually trend toward an intermediate to high pretest probability in the ICU setting. Non-specific tests, like D-dimer assay, have a many false positives and hence a low accuracy in the ICU settings.

MASSIVE PULMONARY EMBOLISM

Acute PE with sustained hypotension [systolic blood pressure <90 mm Hg for at least 15 minutes or requiring ionotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular (LV) dysfunction], pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).

by mansdocs.com

Table 2: Revised Geneva score.

Variable	*Score*
Age 65 years or over	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active malignant condition	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate 75–94 beats per minute	3
Heart rate 95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral edema	4

The score obtained relates to probability of PE:
- 0–3 points indicate low probability (8%)
- 4–10 points indicate intermediate probability (28%)
- 11 points or more indicates high probability (74%)

Table 3: Well's score.

- Clinically suspected DVT—3.0 points
- Alternative diagnosis is less likely than PE—3.0 points
- Tachycardia (heart rate >100)—1.5 points
- Immobilization (≥3 d)/surgery in previous 4 weeks—1.5 points
- History of DVT or PE—1.5 points
- Hemoptysis—1.0 points
- Malignancy (with treatment within 6 months) or palliative—1.0 points

Traditional interpretation:
- Score >6.0—High (probability 59%)
- Score 2.0–6.0—Moderate (probability 29%)
- Score <2.0—Low (probability 15%)

Alternative interpretation:
- Score >4—PE likely (consider diagnostic imaging)
- Score 4 or less—PE unlikely (consider D-dimer to rule out PE)

It accounts for 5% of all cases of PE with at least 15% mortality rate.

Both the Geneva and Pulmonary Embolism Severity Index (PESI) clinical scores identify hypotension (blood pressure <100 mm Hg) as a significant predictor of adverse prognosis.

SUBMASSIVE PULMONARY EMBOLISM

Acute PE without systemic hypotension (systolic blood pressure >90 mm Hg) but with either RV dysfunction or myocardial necrosis is called submassive PE.

- RV dysfunction means the presence of at least one of the following:
  - RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
  - RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT.
  - Elevation of BNP (>90 pg/mL)
  - Elevation of N-terminal pro-BNP (>500 pg/mL) or electrocardiographic changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)
- Myocardial necrosis is defined as either of the following:
  - Elevation of troponin I (>0.4 ng/mL) or
  - Elevation of troponin T (>0.1 ng/mL).

LOW RISK PULMONARY EMBOLISM

Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE are at low risk of PE.

TREATMENT

Empiric Anticoagulation

In patients with no excessive risk of bleeding, empiric anticoagulation is to be strongly considered who are identified as high probablity of PE or, a moderate clinical suspicion for acute PE and the diagnostic evaluation is expected to take longer than 4 hours, or a low clinical suspicion for acute PE and the diagnostic evaluation is expected to take longer than 24 hours.

Anticoagulants act to prevent new clot formation and decrease the risk for recurrent embolism. Empiric anticoagulant therapy should be initiated as soon as possible because its efficacy may be related to achieving therapeutic levels of anticoagulation within the initial 24 hours.

In contrast to the approach for patients with no excess risk for bleeding, empiric anticoagulant therapy should be considered on a case-by-case basis if there is a moderate or high risk of bleeding, or if there are conditions in the differential diagnosis that are contraindications to anticoagulation (e.g. pericardial tamponade, aortic dissection). If anticoagulant therapy is judged to be contraindicated,

by mansdocs.com

the diagnostic evaluation must be expedited so that therapies that do not require anticoagulation (e.g. inferior vena cava filter, embolectomy) can be initiated if acute PE is confirmed.

Among anticoagulants, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and fondaparinux are preferred because of their proven efficacy in patients with PE. Dose adjustments for LMWH are to be done in renal failure, obesity, pregnancy, thrombophilias. UFH is preferred in hemodynamically unstable (massive PE) patients or in whom thrombolytic therapy is being planned. Critically ill patients requiring numerous procedures or having renal failure should preferably be anticoagulated with UFH.

American-Heart-Association recommends the initial use of one of the following regimens:

- Intravenous UFH at an initial bolus of 80 U/kg followed by a continuous intravenous infusion, initially dosed at 18 U/kg/h with dose adjustment to target a partial thromboplastin time between 1.5–2.5 that corresponds to plasma heparin levels of 0.3–0.7 IU/mL) (Table 4).
- LMWH by subcutaneous injection, without routine anti-factor Xa monitoring (regimens such as enoxaparin twice daily at 1 mg/kg or once daily at 1.5 mg/kg, dalteparin once daily at 200 IU/kg or twice daily at 100 IU/kg, or tinzaparin once daily at 175 anti-Xa IU/kg).
- Fondaparinux by subcutaneous injection once daily at 5 mg for patients weighing less than 50 kg, 7.5 mg for patients weighing 50–100 kg, or 10 mg for patients weighing more than 100 kg.

Table 4: Dosing nomogram for unfractionated heparin.

aPTT	*Bolus* (U)*	*Hold (min)*	*Rate change (mL/h)*	*Repeat aPTT† (h)*
<50	5,000	0	+3	6
50–59	0	0	+3	6
60–85	0	0	0	24
86–95	0	0	–2	24
96–120	0	30	–2	6
>120	0	60	–4	6

Note: aPTT indicates activated partial thromboplastin time.

*Heparin infusion based on 20,000 U UFH in 500 mL normal saline, such that 1 mL/h corresponds to 40 U/h. Infusion commenced at 32 mL/h after an initial 5,000-U bolus.

†The first aPTT measurement is made 6 hours after initiation of anticoagulation.

INVESTIGATIONS

In general, patients with clinical suspicion of PE should be investigated with the aim to rule out the other possible differentials diagnosis. The EKG although highly non-sensitive but helps in excluding the other differentials like acute coronary syndrome which may mimic like PE in the multiple presentations. Similarly chest X-ray too has a variable presentation; however, the possible role is justified to rule out other concomitant disorders (e.g. pleural effusion, pneumothorax) which can have the similar presentation.

More specifically the choice of investigations in a suspected case of PE depends upon:

a. Index of suspicion of PE.
b. Hemodynamic stability of the patient.
c. Availability of tests at the center.
d. Sensitivity, specificity and positive predictive value of test.

Patient with high probability of PE and who can be safely moved to the CT room standard for evaluating patients with suspected PE should be subjected to CT pulmonary angiography. Moreover it may also assist in with the other possible important differential and concomitant alternative diagnosis. It also helps in defining the severity of PE by assessing the RV dysfunction and by evaluating the clot burden. However, the accuracy of CT decreases with poor scan quality and more peripheral clots.

Patients with hemodynamic instability should undergo rapid risk stratification to assess for RV dysfunction. If patient has a high probability of PE, bedside echocardiography preferably transesophageal echocardiography (TEE) and lower extremity venous compression ultrasonography (CUS) should be done as soon as possible. ECHO may detect right sided cardiac thrombus or signs of right heart dysfunction associated with PE. ECHO further help in excluding mimics of heart dysfunction associate with PE such acute coronary syndrome, aortic dissection, pericardial tamponade, pulmonary arterial hypertension and congestive heart failure. A patient with massive PE should urgently undergo bedside ECHO assessment. Findings on ECHO that are suggestive of PE are RV dilatation and hypokinesia, increase in RV/LV diameter, pulmonary artery dilatation, tricuspid regurgitation, paradoxical septal motion, inter-ventricular shift toward the LV and McConnell's sign, defined by hypokinesis of the free wall of the RV with normal motion of the apex. In addition, markers of myocardial stress/injury, i.e. BNP, cardiac troponins should also be assessed.

by mansdocs.com

Lower extremity venous CUS may diagnose DVT at bedside. Proximal iliofemoral DVT may serve as a surrogate to PE in the appropriate clinical setting.

D-Dimer assay should be assessed. In case the diagnosis remains uncertain, patient should be sent for multidetector computed tomography-pulmonary angiography (MDCT-PA), once hemodynamically stable.

Radionuclide scintigraphy (V/Q scan) allows bedside testing because of its portability. A ventilation/perfusion scan may be done in patients with high probability of PE and when there is a contraindication for CT such as renal failure and contrast allergy.

If a patient is hemodynamically stable and has a low or medium probability score, then order a high sensitivity D-dimer level. If a high sensitivity D-dimer is negative in low or medium probability, the risk of PE is low (0.14%) and further testing is not warranted.

In pregnant females, concern about the radiation can be negated by the hazard of missing a potentially fatal diagnosis or unnecessary exposing the mother and fetus to the risk prolong anticoagulant therapy. MDCT although delivers a higher dose of radiation to the mother but a lower dose to the fetus than ventilation/perfusion scanning. However, venous USG of legs and 2-D echocardiography can be done before MDCT-PA (Flowchart 1).

THROMBOLYTIC THERAPY PROTOCOL

In contrast to the passive reduction of thrombus size allowed by heparin, thrombolytic agents actively promote the hydrolysis of fibrin molecules. All fibrinolytic drugs approved by the US Food and Drug Administration (FDA) are enzymes that convert the patient's native circulating plasminogen into plasmin. Plasmin is a serine protease that cleaves fibrin at several sites, liberating fibrin-split products, including the D-dimer fragments. Commonly used thrombolytics include streptokinase, urokinase, alteplase (Table 5). Patients with massive PE and submassive PE are the potential candidates where thrombolytic therapy may be warranted, if there is no contraindication to it (Table 6).

Recent surgery, depending on the territory involved, and minor injuries, including minor head trauma due to syncope, are not necessarily barriers to fibrinolysis. The clinician is in the best position to judge the relative merits of fibrinolysis on a case-by-case basis.

- Initiate or continue anticoagulant therapy if it was begun empirically. Consider placement of an inferior vena caval (IVC) filter as an alternative to anticoagulant therapy for patients who have failed anticoagulant therapy, developed complications of anticoagulation, or have an unacceptable bleeding risk.

Table 5: Pharmacological profile of individual fibrinolytic agents and their doses approved by FDA.

Fibrinolytic	*FDA indication for PE?*	*Direct plasminogen activator?*	*Fibrinolytic dose*	*Fibrin specificity (relative to fibrinogen)*	*PAI resistance**
Streptokinase	No	Yes	250,000-IU IV bolus followed by 100,000-IU/h infusion for 12–24 hours	–	–
Urokinase	Yes	No	4,400-IU/kg bolus, followed by 4,400 IU/kg/h for 12–24 hours	–	–
Alteplase	Yes	Yes	100-mg IV infusion over 2 hours	++	++
Reteplase	No	Yes	Double 10-U IV bolus† 30 min apart	+	+
Tenecteplase	No	Yes	Weight-adjusted IV bolus over 5 sec (30–50 mg with a 5-mg step every 10 kg from <60 to >90 kg)	+++	+++

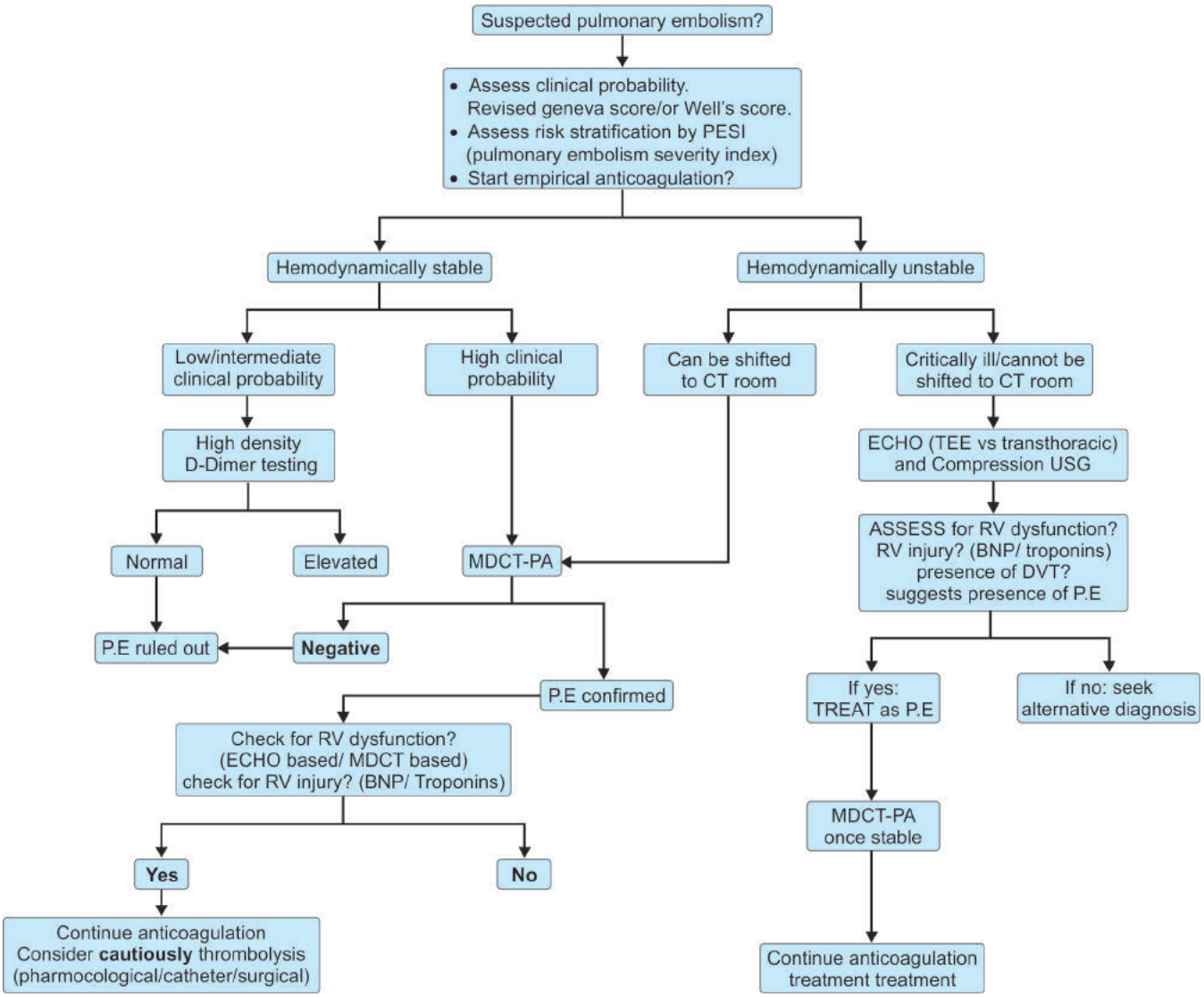
(FDA: US Food and Drug Administration; PE: Pulmonary embolism; PAI: Plasminogen activator inhibitor; IV: Intravenous; +, relative strength + < ++ < +++).

*PAI is a 52-kDa circulating glycoprotein that is the primary native of plasminogen—activating enzymes, and greater PAI resistance confers a longer duration of fibrinolysis.

†Ten units include approximately 18 mg of reteplase and 8 mg of tranexamic acid per dose.

by mansdocs.com

Flowchart 1: Algorithmic approach to a patient with suspected pulmonary embolism



- It should be determined whether the clinical presentation is severe enough to warrant thrombolysis. Embolectomy is appropriate for patients whose presentation is severe enough to warrant thrombolysis, but in whom thrombolysis is either contraindicated or unsuccessful.

IVC Filters

Inferior vena caval filters provide a screen in the inferior vena cava, allowing blood to pass through while large emboli from the pelvis or lower extremities are blocked or fragmented before reaching the lung. Placement of an IVC filter is generally considered in patients who have contraindications to anticoagulation, failed anticoagulation, or developed a complication due to anticoagulation. In addition, IVC filter placement is often considered when the hemodynamic or respiratory compromise is severe enough that another PE may be lethal.

Embolectomy

Embolectomy can be approached via catheters or surgically. It should be strongly considered when a patient's presentation is severe enough to warrant thrombolysis (e.g. refractory hypotension), but thrombolytic therapy either has failed or is contraindicated. Surgical or catheter embolectomy is chosen depends upon the availability of resources and expertise of the institution.

by mansdocs.com

Table 6: Absolute contraindications of thrombolytic therapy.

- Any prior intracranial hemorrhage
- Known structural intracranial cerebrovascular disease (e.g. arteri ovenous malformation), known malignant intracranial neoplasm
- Ischemic stroke within 3 months
- Suspected aortic dissection
- Active bleeding or bleeding diathesis
- Recent surgery encroaching on the spinal canal or brain
- Recent significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury

Relative contraindications to fibrinolysis include:

- Age >75 years
- Current use of anticoagulation
- Pregnancy
- Noncompressible vascular punctures
- Traumatic or prolonged cardiopulmonary resuscitation (>10 min)
- Recent internal bleeding (within 2–4 weeks)
- History of chronic, severe and poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
- Dementia
- Remote (>3 months) ischemic stroke
- Major surgery within 3 weeks

Catheter Embolectomy

Rheolytic embolectomy, rotational embolectomy, suction embolectomy, thrombus fragmentation and ultrasound plus low-dose thrombolytic therapy are techniques that have been utilized to reduce the embolic burden in patients with acute PE.

Surgical Embolectomy

It is generally considered when there is an obvious contraindication to thrombolysis; however, it has also been prompted by echocardiographic evidence of an embolus trapped within a patent foramen ovale, the right atrium or the right ventricle.

Transesophageal echocardiography should be performed before or during pulmonary embolectomy to look for extrapulmonary thrombi (i.e. thrombi in the right atrium, right ventricle or vena cava) which may alter the surgical management.

Surgical embolectomy is typically limited to large medical centers because an experienced surgeon and cardiopulmonary bypass are required.

SUMMARY AND RECOMMENDATIONS

- When a patient presents with suspected acute PE, initial resuscitation should be promptly started. Patients with significant hypoxemia or hemodynamic compromise should be admitted to the intensive care unit.
- Supplemental oxygen should be administered to keep SaO_2 more than 90%. Patients with severe or refractory hypoxemia should be intubated and initiated on mechanical ventilation.
- Judicious fluid therapy has to be early executed in patients who presents with hemodynamic instability. More than 500–1,000 mL during the initial resuscitation period should be administered cautiously as it can further compromise the myocardial function.
- For patients whose hypotension does not resolve with intravenous fluids, prompt vasopressor therapy is recommended. Although norepinephrine is given in the initial phase but combination of dobutamine plus norepinephrine seems to be ideal combination based on their pharmacodynamics profile.
- The decision about whether or not to initiate empiric anticoagulant therapy during resuscitation and the diagnostic evaluation depends upon both the degree of clinical suspicion for acute PE and the risk for bleeding.
- When the diagnostic evaluation exclude acute PE, anticoagulant therapy is discontinued if it was initiated empirically during the resuscitative period and alternative causes of the patient's symptoms and signs are sought.
- When the diagnostic evaluation confirms acute PE, anticoagulant therapy is initiated (or continued if it was begun empirically) and the individual clinical presentation will decide the need for thrombolysis.
- An inferior vena cava filter is an appropriate alternative for patients with confirmed acute PE who have a high risk for bleeding, complications of anticoagulation, recurrent PE despite therapeutic anticoagulation, or hemodynamic or respiratory compromise that is severe enough that another PE may be lethal.
- For patients of acute PE who failed thrombolysis or have contraindications to thrombolysis, catheter or surgical embolectomy should be considered. The decision of whether to pursue one of these approaches should be based upon local expertise.

by mansdocs.com

BIBLIOGRAPHY

1. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of sus-pected acute pulmonary embolism. Thorax. 2003;58: 470-84.
2. Kearon C, et al. American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (published correction appears in Chest. 2008;134:892). Chest. 2008; 133(Suppl):454S-545S.
3. Lloyd-Jones D, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2010 update: a report from the American Heart Association (published correction appears in Circulation. 2010;121:e260). Circulation. 2010;121:e46-215.
4. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association. Circulation. 2011;123:1788-830.
5. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA. 1990;263:2753-9.
6. Sharifi M, Bay C, Skrocki L, et al. Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111:273-7.
7. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315.

by mansdocs.com

CHAPTER

21

Intensive Care Unit Management of Patients with Right Heart Failure

Harjit Dumra

INTRODUCTION

The right ventricle (RV) is a thin-walled, crescent-shaped structure that is adapted to eject into the pulmonary circulation; a circuit characterized by low resistance, high compliance, and low impedance. The right and left ventricle (LV) are interrelated by the shared interventricular septum. Although highly efficient, the naive RV poorly adapts to sudden increases in afterload. An increase in RV end-diastolic volumes initially improves cardiac output (CO) by the Frank-Starling mechanism, but a severe and sudden increase in RV afterload may overwhelm the contractile capability of the RV and lead to hemodynamic collapse (Flowchart 1).

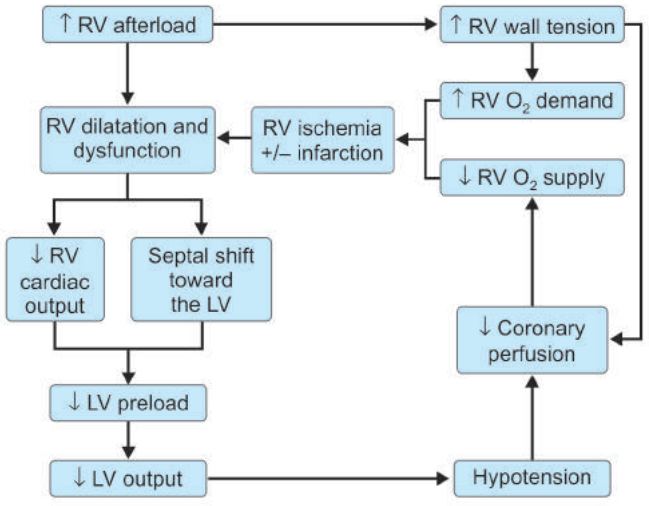
Right ventricular failure (RVF) remains a real clinical challenge for cardiologists, intensive care unit (ICU) and emergency physicians. Very often it is difficult to manage due to hemodynamic instability and serious comorbidities.

Pulmonary hypertension, a common precursor to RVF is frequently encountered in the critically ill. Pulmonary hypertension is more usually a consequence of another acute condition, rather than the cause of admission into ICU. However, this situation is often unrecognized or underestimated in ICU patients, although its impact on outcome is important.

Pulmonary hypertension and RVF are intricately linked and acute or acute on chronic worsening in pulmonary hypertension, constitutes the most common cause of RVF in the ICU. RVF is also the most common cause of death in patients with pulmonary hypertension, and RV function is the major determinant of morbidity and mortality in this patient population. Hence identifying the cause of pulmonary hypertension is integral to managing RVF.

For decades, left ventricle has been much more studied, and most therapeutic measures for treatment of acute heart failure were focused on left ventricular (LV) failure. Till date, there is no guideline or consensus statement on the management of pulmonary hypertension or right heart failure in the critically ill. Although several reviews have been published, the management in the specific setting of ICU is mainly based on expert opinion.

Flowchart 1: Hemodynamic changes in right ventricular failure.



by mansdocs.com

As the main cause of death in critically ill patients with pulmonary hypertension is RVF and its consequences, the management of these patients includes two parts:

1. The first consists of treating the symptoms to avoid RVF or at least to limit its consequences
2. Parallely treating the cause of the pulmonary hypertension.

DEFINITION

An acceptable definition of right heart failure is, a clinical syndrome resulting from the inability of the right ventricle to provide adequate blood flow to the pulmonary circulation at a normal central venous filling pressure. Clinically, RVF is characterized by a reduced cardiac output (CO i.e. cardiac index < 2.5 L/min/m^2) and an elevation in RV filling pressure (i.e. right atrial pressure > 8 mm Hg).

ETIOLOGY AND PATHOPHYSIOLOGY OF RIGHT VENTRICULAR FAILURE

Right ventricular failure results from any structural or functional process decreasing the ability of the RV to pump blood into the pulmonary circulation. Causes include alterations in preload and diastolic filling, decreases in inotropy, and increases in afterload.

RV preload and diastolic filling affect myocardial fiber length and contractility via the Frank-Starling mechanism, and both increases as well as decreases in preload may negatively affect RV function (Table 1).

The most common etiologies of RVF in the ICU are:

- LV failure
- RV ischemia
- Acute pulmonary embolism
- Pulmonary hypertension
- Sepsis
- Acute lung injury
- Cardiac tamponade
- Postcardiothoracic surgery states.

Arrhythmias and pericardial, congenital, and/or valvular heart disease may also contribute to the development of right heart failure. Acute RVF is also observed during acute chest syndrome in patients with sickle cell disease.

The classic picture of RVF with low CO and elevated RV filling pressures is typically seen in patients with pulmonary hypertension. The most frequent cause of pulmonary hypertension in critically ill patients is pulmonary hypertension associated with LV failure secondary to an increase in left atrial pressure. Another common cause is the worsening of a chronic pulmonary arterial hypertension (PAH–Group I Pulmonary Hypertension), whereas acute pulmonary hypertension in patients without preexisting pulmonary hypertension occurs mostly in the case of massive pulmonary embolism, acute respiratory distress syndrome (ARDS) and sepsis.

A reduction in oxygen delivery in PAH also contributes to RV dysfunction. This may result from either a decrease in LV filling due to reduction in pulmonary blood flow or the RV enlargement may lead to reduced LV filling mediated by septal wall motion displacement by a pressure and volume overloaded right ventricle.

Table 1: Cause of acute right ventricular failure (RVF).

Left ventricular failure	• Ischemic heart disease, valvular heart disease, etc.
RV ischemia	• RV infarction • Relative due to RV pressure and/or volume overload
Afterload increase	• Pulmonary artery hypertension (primary and secondary) • Hypoxic pulmonary vasoconstriction • Postcardiothoracic surgery • Pulmonary embolism • Pulmonary microthrombi (sepsis and acute lung injury) • Pulmonary stenosis and RV outflow tract obstruction • Mechanical ventilation • Acute chest syndrome in sickle cell disease
Preload decrease	• Hypovolemia/capillary leak • Superior vena cava syndrome • Tricuspid stenosis • Cardiac tamponade • Mechanical ventilation
Myocardial disease	• Cardiomyopathies • Arrhythmogenic RV dysplasia • Sepsis
Congenital and valvular heart disease	• Ebstein's anomaly • Tetralogy of Fallot • Transposition of great arteries • Atrial septal defect • Anomalous pulmonary venous return • Tricuspid regurgitation • Pulmonary regurgitation • Mitral valve disease
Pericardial disease Arrhythmias	• Constrictive pericarditis

by mansdocs.com

Also, the enlargement of RV leads to prolongation of RV contraction, causing RV contraction to continue beyond LV contraction, with resultant RV systolic encroachment on LV filling.

RV ischemia also contributes to RV failure. Normally RV is perfused in both systolic and diastolic phases as a result of the low systolic pressure (25 mm Hg), which does not occlude the vessel that has a systemic pressure. Once afterload increases following PH, pressure necessary to contract the RV successfully also increases, leading to partial occlusion of the right coronary artery (RCA) eventually results in RV ischemia and hemodynamic collapse

It is important to recognize that in this adverse situation, volume loading may paradoxically lead to a reduction in LV filling. Conversely, a reduction in RV volume (mediated through diuresis) may improve left ventricular filling and CO by reducing influence of septal displacement.

In this volume overloaded state both RV filling and LV filling are also highly susceptible to the deleterious effects of tachycardia and tachyarrhythmia, which may further reduce LV filling and stroke volume.

Factors Affecting Right Ventricular Function in ICU

In the majority of these conditions, RV dysfunction prognosticates worse outcomes. The pathophysiology of acute RVF in critically ill patients is complex and includes ischemia and/or arrhythmias, endotoxin and cytokine-induced decreases in systolic and diastolic LV and RV function, as well as afterload increases from endothelial dysfunction, hypoxic pulmonary vasoconstriction (HPV), and pulmonary microthrombi and/or thromboemboli. LV dysfunction, either cytokine-induced or due to ischemia or nonischemic cardiomyopathies, induces RV dysfunction via afterload increase, and/or displacement of the interventricular septum toward the RV with subsequent impairment of RV filling (known as ventricular interdependence).

Hypovolemia and inflammation-induced capillary leak alter RV function by decreasing preload (Fig. 1). Important interactions between inflammation, sepsis, pulmonary endothelial dysfunction with associated pulmonary hypertension, lead to RV and LV dysfunction.

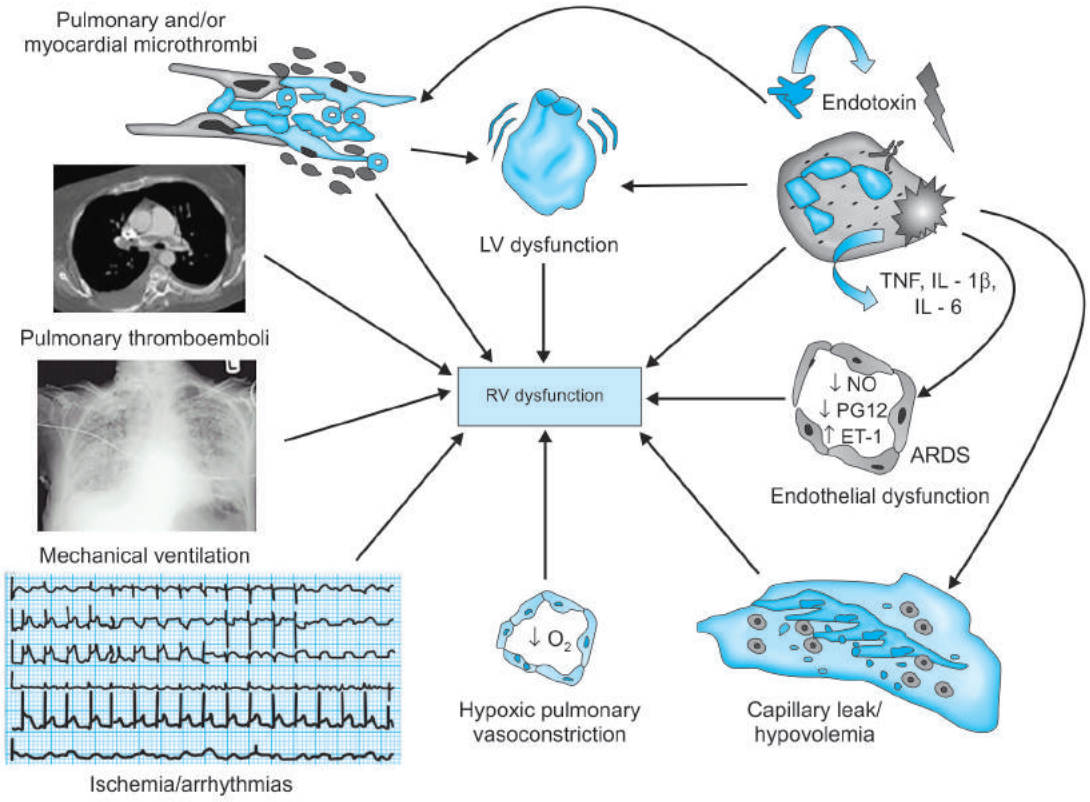


Fig. 1: Pathophysiologic changes seen in right ventricular (RV) failure.

by mansdocs.com

Proinflammatory cytokines like tumor necrosis factor directly suppress myocardial contractility. Heightened oxygen demands from increased heart rate, afterload, and wall tension, combined with decreased coronary perfusion from hypotension, result in subendocardial and myocardial RV ischemia. Mechanical ventilation, certain drugs, and volume overload may further alter RV function.

Monitoring of Right Ventricular Function in the ICU

Diagnostic methods of RVF include pulmonary artery catheterization (PAC), echocardiography (either transthoracic or transesophageal), and sometimes, cardiac magnetic resonance imaging.

There is no gold standard method of monitoring RV function in the ICU.

Pulmonary Artery Catheterization (PAC)

Although, many advocate for the use of invasive pulmonary hemodynamic monitoring it is unclear if an approach guided by changes in pulmonary hemodynamics translates into improved outcomes. In addition, there are both practical and theoretical limitations to the use of pulmonary hemodynamics to guide treatment. The measurement of thermodilution CO in the setting of severe tricuspid insufficiency may be problematic. Additionally, the use of the indirect Fick method (using an assumed value for oxygen consumption) may be inaccurate as it will not incorporate changes in oxygen consumption with changes in treatment or metabolic rate. The severity of pulmonary hypertension cannot be reliably assessed by the degree of elevation in pulmonary pressures as a failing ventricle will produce lower pressures as it fails. Furthermore, the reliance on pulmonary vascular resistance (PVR) as a measure of disease severity or prognosis may also be problematic.

Echocardiography

Even if pulmonary artery catheter remains the gold standard to appreciate the level and the mechanism of pulmonary hypertension and right heart failure, echocardiography is most often used in clinical settings to evaluate critically ill.

It provides essential information about right ventricle geometry and function and also permits intermittent repetitive follow-up of the dynamics of therapeutic responses. It allows direct and noninvasive visualization of the right ventricle and represents an accurate tool for evaluating RV function at the bedside. Echocardiography also provides information about possible associated precipitating factors of RVF, such as pericardial effusion with or without tamponade, tricuspid insufficiency, or RV ischemia. Additionally, echocardiography enables the simultaneous evaluation of LV function, a possible component of the RVF.

Although, there are several echocardiographic measures of RV performance that have correlated with prognosis, it is unclear if these can be used in the acute setting. Tricuspid annular displacements during RV systole, Tei index, and eccentricity index have all been correlated to RV function and prognosis in the outpatient setting. However, test characteristics such as reliability, reproducibility, and diagnostic accuracy as a maker of RV function have not been formally evaluated in the critical care setting. Additionally, practical limitations may preclude obtaining accurate images to make these measurements. Similar to the caveat with following pulmonary arterial pressures, there are pitfalls to the use of RV systolic pressure as a marker of RV function and as a goal of treatment in the acute setting.

Cardiac Magnetic Resonance Imaging

Although, magnetic resonance imaging is considered the gold standard of evaluating RV function it is not practical in unstable patients. Whether newer echocardiographic modalities of measuring RV volume and right ventricular ejection fraction (RVEF) can be used in the critical care environment needs evaluation.

Evaluation of cardiac function as well as end-organ function is critical in managing patients with RV failure. Measurements of renal, liver, and neurological function will provide some information about the adequacy of cardiac function and tissue perfusion.

Biomarkers

Although in the setting of chronic pulmonary hypertension, it has been shown that elevated natriuretic peptides and elevated troponin levels were associated with worst outcome; interest in biomarkers for the diagnosis and the management of critically ill patients with pulmonary hypertension is supported by several publications, in particular in the setting of pulmonary embolism.

Thus, brain natriuretic peptide (BNP) and troponin I led to stratifying patients with pulmonary embolism regarding the risk of development of RVF. It has been also

by mansdocs.com

shown that elevated troponin I at admission in patients with acute pulmonary embolism was an independent predictor of in-hospital death and also independently associated with a higher risk for the development of RV dysfunction and cardiogenic shock.

Finally, it has been shown that BNP is a prognostic factor in patients with severe pulmonary hypertension, but its clinical relevance in the setting of critical care remains unclear.

TREATMENT OF RIGHT VENTRICULAR FAILURE

The management of RV failure in patients is complex and requires expertise.

RV failure eventually results in multiorgan dysfunction. Reduced cardiac function can result in decreased bowel perfusion, loss of the intestinal barrier function, and bacterial translocation, a complication that has been implicated as a common cause of death in these patients.

Reduced hepatic perfusion can impair liver function or may even result in liver failure.

Renal failure is another disastrous complication of RV failure.

The initial focus of care should center on addressing any potential reversible cause of acute RV decompensation and development of a strategy to improve RV function. The latter may be achieved through modifying RV preload, contractility, and afterload. Consideration must also be given to maintaining coronary perfusion and avoiding tachycardia.

General Supportive ICU Care

Infection prevention measures, thromboembolism and peptic ulcer prophylaxis, early nutritional support, glucose control, and (in stable mechanically ventilated patients) daily interruptions of sedation combined with spontaneous breathing trials should be applied to all patients with acute RVF. The optimal hemoglobin level for patients with acute RVF remains to be determined. Although ICU patients usually benefit from a conservative transfusion strategy, patients with shock or heart failure may require higher hemoglobin levels. This might be the case for patients with acute RVF as well. Clearly, significant anemia in the setting of decreased tissue oxygenation should be corrected. Hemoglobin levels greater than 10 g/dL are preferred. Sodium restriction (in volume overload states) and daily monitoring of body weight and volume status are indicated.

Strategies to Improve Right Ventricular Function (Flowchart 2)

Interventions that Optimize Volume Status, Minimize Hypoxic Pulmonary Vasoconstriction and Target Arrhythmias:

As RV function is highly volume dependent, a careful balance between optimized pre-load and decreased afterload is essential. If pre-load is too low, RVEF will not be adequate. However, too much preload will cause the intraventricular septum to shift leftward, decrease LV output, and cause hypotension through ventricular interdependence, especially in the setting of high intrathoracic pressures or pericardial disease. Therefore, careful administration of fluid boluses, used in conjunction with noninvasive or invasive assessment of CO, is recommended (Table 2).

Vigorous fluid administration may be detrimental and should be discouraged. Diuretics are indicated for volume overload. Due to its potential for greater weight and fluid loss than intravenous diuretics, venovenous ultrafiltration is increasingly used for decompensated left heart failure. Whether this represents a feasible option in diuretic-resistant right heart failure needs further study.

Adequate oxygenation is of utmost importance to avoid afterload increases due to hypoxic pulmonary vasoconstriction (HPV). Hence the target is to maintain oxygen saturations of more than 92%.

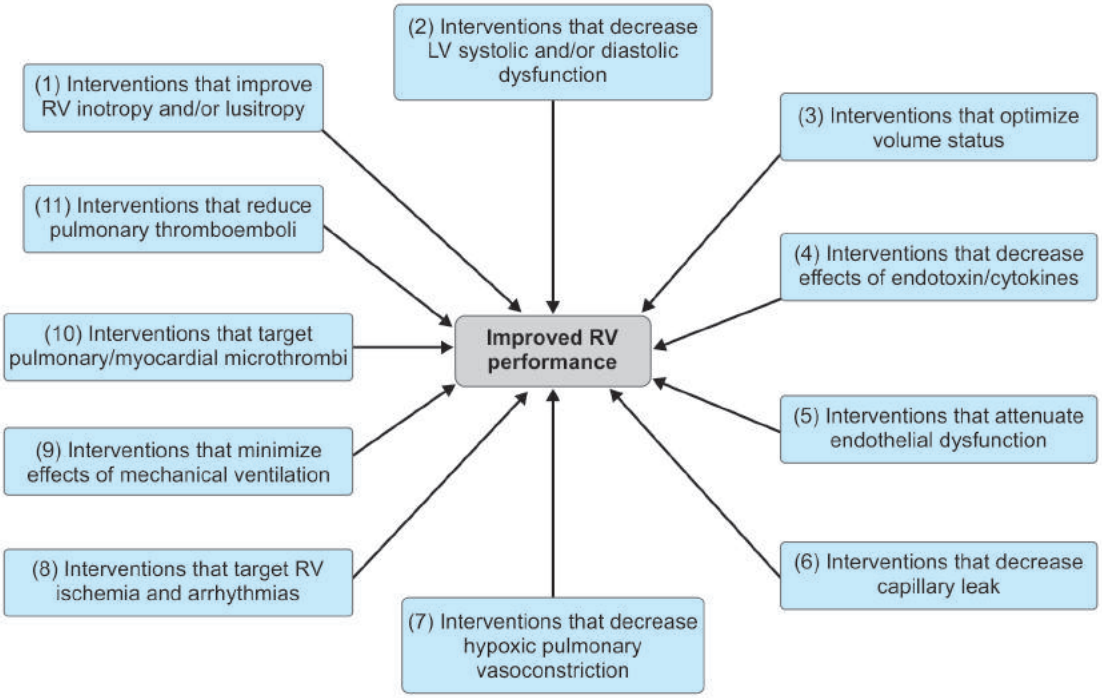
As the RV is extremely susceptible to alterations in cardiac rhythm and ventricular synchrony, restoration of sinus rhythm and/or atrioventricular synchrony makes sense, but few studies have focused on this matter in acute RVF specifically. Clearly, hemodynamically significant bradycardias or tachyarrhythmias should be corrected. Digoxin marginally improves CO in patients with severe pulmonary hypertension in the short term. However, due to potential side effects and a narrow therapeutic window, routine use is discouraged. Beta-blocking agents and angiotensin-converting enzyme inhibitors improve RV hemodynamics in patients with biventricular failure and have theoretical benefits in isolated RVF, but their role in the latter is poorly studied.

Interventions that Minimize Effects of Mechanical Ventilation

Every attempt should be made to avoid endotracheal intubation in patients with RV failure. Intubation of these patients is often problematic owing to effects of sedatives on cardiac function and nonselective vasodilation leading to systemic hypotension and hemodynamic collapse.

by mansdocs.com

Flowchart 2: Interventions to improve right ventricular performance.



Continuous positive airway pressure or noninvasive ventilation may be considered, but opioids or sedatives should be administered with great care to avoid drops in blood pressure. If intubation and mechanical ventilation are unavoidable, hypotension and loss of RV contractility must be prevented and the administration of catecholamines before anesthesia should be considered. Despite the lack of controlled clinical trials, etomidate is the preferred drug for induction of general anesthesia as it has little effect on cardiac contractility and vascular tone. Maintenance of anesthesia is usually achieved with low-dose opioids or ketamine together with benzodiazepines or propofol.

Due to potential adverse hemodynamic effects, mechanical ventilation needs to be administered with caution and expertise. Higher tidal volume (VT) and positive end-expiratory pressure (PEEP) may increase pulmonary artery pressure (PAP) and right atrial pressure (RAP), worsen tricuspid regurgitation, and increase RV afterload. In addition, PEEP may decrease pre-load by diminishing venous return. Therefore, the lowest VT, plateau pressure, and PEEP needed to provide adequate ventilation and oxygenation should be used. Lower VT may also decrease cytokine-induced endothelial dysfunction. However, because permissive hypercapnia can increase PAP and worsen RVF through vasoconstriction, excessive hypercapnia should be avoided. Hyperventilation, on the other hand, attenuates acidosis-induced vasoconstriction and decreases PAP. Hyperventilation can be used to lower PAP acutely, but should not be performed at the expense of a high VT. Because increases in respiratory rate can cause dynamic hyperinflation and increased intrathoracic pressures, airway pressures and flow-time loops should be watched closely.

Prone ventilation, although not affecting mortality in acute lung injury, may unload the RV through effects on airway pressure and improved alveolar ventilation. The effects of high-frequency oscillatory ventilation on RV function are poorly defined, although decreases in CO are described. Although transient improvements in oxygenation may also be achieved with recruitment maneuvers, these may cause decreased venous return and hypotension and should therefore only be used with extreme caution when significant hypoxemia is present.

Interventions that Improve RV Inotropy and Increase RV Perfusion Pressure

Inotropes improve cardiac contractility and CO by increasing cyclic adenosine monophosphate. Vasopressors increase RV perfusion pressure, thereby attenuating

by mansdocs.com

Table 2: Overview of serum markers, hemodynamic parameters, and echocardiographic variables used in the diagnosis of acute right ventricular (RV) failure in the intensive care unit.

BNP, NT-proBNP, troponin	• Increase in LV dysfunction, renal failure, sepsis, but significant RV dysfunction less likely if values normal BNP predicts survival in acute RVF in PAH; increased levels (1,415 pg/mL vs 628 pg/mL) associated with increased mortality • BNP > 168 pg/ml identifies RV dysfunction in CTEPH patients with 88% sensitivity, 86% specificity. Risk stratification in patients with subtle RV dysfunction during acute, nonmassive PE
Sodium	• ≤ 136 mmol/L predicts RVF and increased risk of death in PAH patients • Predicts survival in PAH patients with acute RVF; decreased levels associated with increased mortality
Creatinine	• Predicts survival in PAH patients with acute RVF; increased levels (4 mg/dl vs 1.2 mg/dL) associated with increased mortality
C-reactive protein	• Predicts survival in PAH patients with acute RVF; increased levels (4 mg/dl vs 1.2 mg/dl) associated with increased mortality (14)
Transaminases	• Increase reflects hepatic congestion and/or hypoperfusion due to compromised LV function and forward failure. Prognostic value not established
Growth differentiation factor-15	• Stress responsive, transforming growth factor-beta-related myocardial cytokine • Independent predictor of long-term mortality in acute PE; increased value of established prognostic markers • Risk stratification in PAH patients; increased levels associated with increase in markers of RV dysfunction
Right atrial pressure, cardiac index	• Strongest hemodynamic prognosticators in PAH (22); more accurate reflection of RV function than PAP • Right atrial pressure ≥ 15 mm Hg, cardiac index ≤ 2 L/min/m^2 indication for transplantation referral in PAH
PVR	• Differentiates whether increased afterload is due to PAH, secondary PH, or hyperdynamic states • PVR > 1,000–1,200 dynes sec cm^5; contraindication for atrial septal defect closure, balloon atrial septostomy in severe PAH, pulmonary endarterectomy in CTEPH
Right ventricular stroke work index	• Prognosticates RVF after LVAD placement and transplantation-free survival in dilated cardiomyopathy • Easily obtained via PAC; may allow for further prognostication in acute RVF, but further studies needed
Pulmonary artery impedance	• Evaluates and integrates PVR and pulmonary artey elastance, flow, pulsatile pressure, and wave reflection • Superior and more complete method of RV afterload assessment than PVR alone
RVEF, RA and RV volume, tricuspid regurgitation, ventricular septal shift, pericardial effusion	• Established and readily available markers of RV dysfunction • Limited by marked preload dependence
Right ventricular systolic pressure	• Calculated from tricuspid regurgitant jet and RAP; cannot be obtained if no regurgitant jet identified off by > 10 mm Hg in almost 50% of measurements in PAH patients
TAPSE, tissue Doppler, Tei index	• More specific and less pre-load-dependent than traditional echocardiographic markers, • Established prognostic value of TAPSE in PAH patients; significantly decreased survival if TAPSE < 1.8 cm

(BNP: B-type natriuretic peptide; CTEPH: Chronic thromboembolic pulmonary hypertension; LV: Left ventricular; LVAD: Left ventricular assist device; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PAC: Pulmonary artery catheter; PAH: Pulmonary arterial hypertension; PAP: Pulmonary artery pressure; PE: Pulmonary embolism; PH: Pulmonary hypertension; PVR: Pulmonary vascular resistance; RA: Right atrial; RV: Right ventricular; RVF: Right ventricular failure; RVEF: Right ventricular ejection fraction; TAPSE: Tricuspid annular plane systolic excursion).

subendocardial ischemia. All inotropes concomitantly target the left ventricle (a desired effect in LV failure-induced RVF).

Dobutamine: This inotrope traditionally used in cardiac pump failure, works through B1-receptor–mediated increases in myocardial contractility. Concomitant B2 stimu-

by mansdocs.com

lation induces vasodilation and decreases afterload. In acute PH, low-dose dobutamine (2 to 5 μg/kg/min) increases CO and decreases PVR, whereas higher doses (5 to 10 μg/kg/min) only induce tachycardia and increase myocardial oxygen consumption without further improvements in PAP. In acute and chronic PH, the combination of dobutamine and inhaled nitric oxide (iNO) improved CO, decreased PVR, and increased the PaO_2/FiO_2 ratio. However, dobutamine may cause hypotension through peripheral B2 stimulation, sometimes requiring the addition of a peripheral vasoconstrictor (e.g. norepinephrine).

Milrinone: It is a selective phosphodiesterase (PDE)-3 inhibitor that exerts inotropic and vasodilatory properties. Although decreasing PVR and increasing RVEF in acute and chronic PH, use is limited by systemic vasodilation and hypotension. Like dobutamine, milrinone can be combined with iNO to augment pulmonary vasodilation while minimizing hypotension and tachyarrhythmias. Inhaled milrinone minimizes hypotension but maintains beneficial effects on PVR and RVEF and even attenuates pulmonary endothelial dysfunction. However, due to relatively selective PDE-5 expression in the lung and hypertrophied RV, PDE-5 inhibitors may be more effective and more pulmonary artery and RV specific than PDE-3 inhibitors.

Norepinephrine: It increases inotropy through B1 agonism. Concomitant stimulation of A1-receptors increases RV perfusion pressure and CO as seen in a model of acute pulmonary embolism–induced RVF. Concerns about increases in PVR and PAP exist, however are not proven. Norepinephrine may therefore be beneficial in hypotensive and tachycardic patients not tolerating dobutamine, but the latter remains the preferred inotrope for PH and/or acute RVF without significant hypotension

Levosimendan: It sensitizes cardiac troponin C to the effects of intracellular calcium, thereby increasing contractility without increasing oxygen consumption. Levosimendan also has global vasodilatory and anti-ischemic properties that are mediated by activation of adenosine triphosphate sensitive potassium channels in mitochondria of vascular smooth muscle cells and by endothelin-1 inhibition. The drug increases CO, decreases PVR, and improves regional perfusion, together with a protective effect against endothelial dysfunction by inhibiting expression of soluble adhesion molecules. Levosimendan attenuates injury induced RV and LV dysfunction and increases regional blood flow and global oxygen transport. Although sharing the vasodilatory effects of dobutamine and milrinone, it seems to have more specific pulmonary vasodilatory properties. Certain studies have demonstrated decreased afterload and increased RV contractility with levosimendan superior to those of dobutamine.

Interventions that Decrease RV Afterload (Pulmonary Vasodilators)

Because the RV poorly tolerates afterload increases and because pulmonary hypertension is a common cause of RVF, pulmonary vasodilators represent cornerstones of RVF treatment. All systemically administered pulmonary vasodilators can cause hypotension and need to be initiated cautiously. Also most of the data pertaining to use of pulmonary vasodilators pertains to right heart failure following PAH (Group I Pulmonary Hypertension) and hence cannot be extrapolated to using them in pulmonary hypertension secondary to other causes.

Inhaled Nitric Oxide (iNO): It mediates pulmonary vasodilation by increasing cyclic guanosine monophosphate. Rapid inactivation by hemoglobin in the pulmonary capillaries prevents systemic vasodilation. Effects are limited to ventilated areas of the lung, therefore helps in attenuating HPV, decreasing PAP and PVR, and improving oxygenation without increasing intrapulmonary shunt fraction (unlike systemically administered pulmonary vasodilators, which may aggravate hypoxemia in patients with lung disease). In addition, iNO decreases inflammatory cytokine production. Use of iNO is limited by potential methemoglobinemia, production of reactive nitrogen species, and rebound PH after rapid discontinuation. Also it is not available in most centers in India. iNO may be of particular benefit when combined with inodilators (dobutamine or milrinone)

Prostacyclins: They activate cyclic adenosine monophosphate, resulting in pulmonary and systemic vasodilation and inhibition of platelet aggregation. Although improving end points in pulmonary arterial hypertension (PAH), prospective data on critically ill patients with acute RVF are sparse. The short half-life (3–6 min) and its potent effects make epoprostenol the preferred prostacyclin in the ICU. Initiated at 1–2 ng/kg/min, the drug is increased by 0.5–1 ng/kg/min every 15–30 min. A more cautious approach is often warranted in critically ill patients with significant comorbidities, hypoxemia, and/or labile hemodynamics. Epoprostenol decreases PAP and PVR and increases CO, but its use is limited by dose-dependent side effects (e.g. hypotension, gastrointestinal symptoms, and headaches). It should be avoided in respiratory

by mansdocs.com

failure, shock, and LV dysfunction. Similar to iNO, abrupt discontinuation may lead to rebound PH and even death. Nebulized or inhaled prostacyclins forgo systemic side effects, representing an attractive alternative to iNO. No special equipment is required for administration or toxicity monitoring. Inhaled iloprost for RVF is supported by experimental and clinical data. Iloprost improves PH and RV function in patients undergoing mitral valve surgery, cardiopulmonary bypass, or heart transplantation and may be more potent than iNO. Treprostinil decreases PAP and PVR, but its use in the ICU is limited by a longer half-life than that of epoprostenol. In unstable patients, intravenous or inhalational administration is preferred over the subcutaneous route because the latter may be limited by unpredictable absorption. Inhaled treprostinil (15 or 30 μg) additively decreased PVR and PAP and increased CO when added to sildenafil in a recent open-label trial in PH patients. Prostacyclins are presently not available in India.

Endothelin receptor antagonists (Bosentan/Ambrisentan): They block endothelin-A and -B receptors in vascular smooth muscle and endothelial cells, attenuating endothelin's vasoconstrictive, proliferative, and proinflammatory effects. Although increasing CO and decreasing PAP in PH patients, endothelin receptor antagonist use in the ICU is limited by relatively long half-lives (5 h for bosentan) and potential hepatotoxicity, the latter occurring less frequently with selective endothelin-A receptor antagonist, Ambrisentan.

PDE-5 inhibitors (Sildenafil/Tadalafil): They block degradation of cyclic guanosine monophosphate. They decrease PAP and increase CO in both acute and chronic PH and may be particularly beneficial for HPV. Few studies investigated PDE-5 inhibitors in ICU patients. In a study in patients undergoing mitral valve repair or LV assist device (LVAD) placement, sildenafil decreased PAP and PVR and facilitated weaning of inhaled and intravenous pulmonary vasodilators while only minimally decreasing systemic blood pressure. In LVAD patients, sildenafil facilitated weaning from iNO and inotropes and provided additional decreases in PAP. Sildenafil or its analog decrease PVR, maintain systemic vascular resistance, and improve myocardial perfusion after coronary artery bypass grafting. Sildenafil also has unique lusitropic and/or ino-tropic effects in the hypertrophied RV, the latter being exerted through PDE-3 inhibition (milrinone-like effect). Furthermore, sildenafil decreases RV mass in PAH patients. The drug also improves pulmonary hemodynamics and exercise capacity in patients with systolic LV dysfunction. Hemodynamic effects of sildenafil occur after 15–30 min, with peak effects after 30–60 min, and a half-life of 4 h.

The use of PAH-targeted therapies depends primarily on previous treatment. In therapy-naive patients with PAH and RV failure, intravenous prostacyclin derivatives (epoprostenol, treprostinil, iloprost) are the initial treatment of choice, although care must be taken to avoid systemic hypotension. Once these patients have been stabilized, oral therapies with endothelin receptor antagonists and PDE-5 inhibitors may be added with or without later withdrawal of the prostanoid. Intravenous prostacyclin derivatives are also the preferred therapy for patients who have been pretreated with nonparenteral drugs, although the clinical response is sometimes less impressive than in treatment-naive patients.

Inhaled vasodilators such as NO or iloprost might be used as supplementary therapy, especially in patients who do not tolerate parenteral prostanoids because of systemic hypotension.

Role of mechanical interventions: The presence of large pericardial effusions is associated with a poor prognosis in patients with pulmonary arterial hypertension, but the presence of tamponade may be difficult to determine on the basis of typical echocardiographic criteria. In general, draining pericardial effusions should be avoided. Although anecdotal case reports suggest that opening of the pericardium may improve cardiac function, two small series reported 50% mortality in patients who had their effusion drained.

Balloon atrioseptostomy (BAS) is used in some pulmonary hypertension centers as treatment of severe pulmonary hypertension. BAS decompresses the enlarged RV and improves LV filling as well as cardiac output. Despite oxygen desaturation, the net effect is usually an increase in systemic oxygen transport. In experienced centers BAS is considered a safe procedure as long as it is performed in hemodynamically stable patients. However, BAS is not recommended as an emergency procedure for patients with RV failure, as the risk of fatal complications is high in patients with markedly elevated RV-filling pressures (RA pressure > 20 mm Hg) and/or low oxygen saturations (not recommended for patients with O_2 saturation at rest < 80% on room air).

In RVF due to chronic thromboembolic PH, pulmonary thromboendarterectomy improves New York Heart Association functional class, exercise tolerance, and survival. The best outcomes are achieved in patients with proximal angiographic PA obstruction and absent or minimal small vessel disease and if the postoperative PVR can

by mansdocs.com

be decreased to, < 500 dynes·sec·cm^2. Surgical embolectomy is used for acute massive pulmonary embolism when thrombolysis fails or is contraindicated. Percutaneous mechanical approaches with or without intrapulmonary thrombolytics can be used in this setting, but comparison of this approach with medical or surgical thrombolysis are sparse. The treatment guidelines discussed above are summarized in Flowchart 3.

LUNG TRANSPLANTATION, BRIDGING, AND EXTRACORPOREAL LIFE SUPPORT (ECLS)

Despite advances in medical therapy, lung or heart–lung transplantation (H/LTx) remains an important treatment option for patients with progressive PH, especially for patients with refractory RV failure.

For patients requiring ICU care for PAH and RV failure, several important decisions regarding transplantation need to be made:

1. Is the patient suffering from end-stage RV failure not responding to optimized medical therapy?
2. Provided the answer to the first question is yes, is the patient a potential candidate for H/LTx, and is it possible to realize transplantation in a reasonable time frame (what is reasonable will depend on patient factors as well as local organ allocation rules and organ availability)?
3. If the answer to the second item is also yes, may the patient benefit from extracorporeal life support (ECLS)?

Once a decision to proceed with H/LTx has been made, ECLS becomes a bridging strategy. Maintaining cardiac output and preventing secondary organ failure are the most important objectives of ECLS.

With appropriate ECLS, the RV is immediately unloaded; PAH therapy and catecholamines are usually no longer required; and the perfusion of other organs, especially bowel, liver, and kidneys, dramatically improves. ECLS should therefore be considered in patients with refractory hypotension and/or signs of progressive secondary organ dysfunction, at least when prompt transplantation is a realistic option.

Pumpless Lung Assist Devices Inserted into the Pulmonary Circulation

An alternative bridging strategy is the use of a pumpless device inserted between the pulmonary arteries and the left atrium (PA–LA). The first report on the successful application of the PA–LA approach was published by groups from Germany and Canada. They used an interventional lung assist device designed by Novalung (Hechingen, Germany), a low-resistance membrane oxygenator, originally developed for insertion between a femoral artery and a femoral vein to allow extracorporeal CO_2 removal. In patients with PAH, the device was connected between the main pulmonary artery and the left atrium. The patient's RV drives blood flow through the device, thus obviating the need for a pump.

The insertion of this device requires general anesthesia, intubation, mechanical ventilation, and sternotomy. The centers using this technique so far prefer to place the patients on veno-arterial extracorporeal membrane oxygenation (ECMO) before the procedure to avoid hemodynamic instability after intubation. The ECMO cannulas are later removed once blood flow through the Novalung device has been established. As with VA ECMO, this approach results in immediate stabilization of hemodynamics and gas exchange. Most of the patients can be extubated after the procedure. The insertion of the PA–LA device is more elaborate than implanting a VA ECMO. However, the PA–LA approach requires no blood pump and the patients can be fully mobilized. In addition, this technique leads to reconditioning of the deprived and stiff left ventricle, which may help to avoid complications after the transplantation.

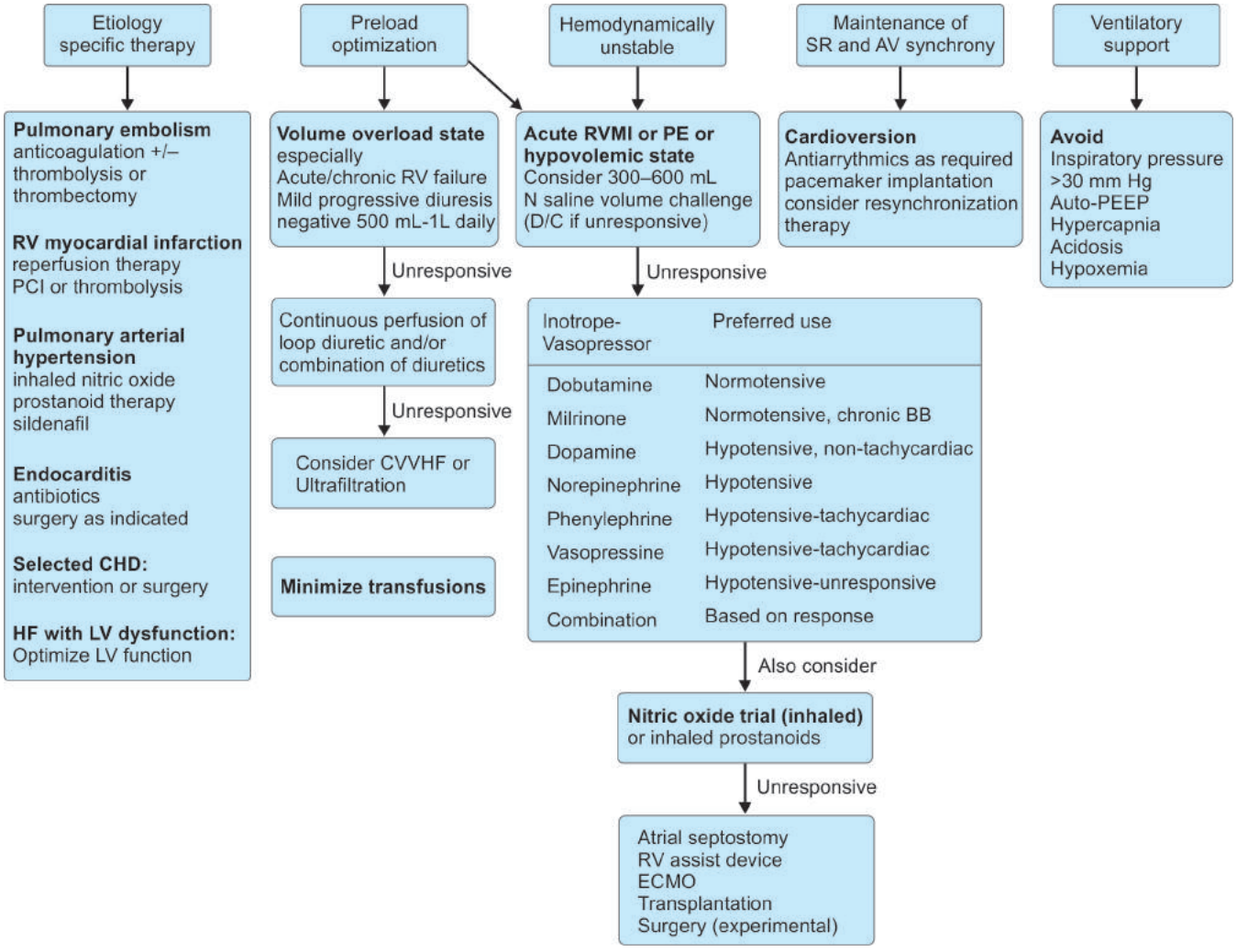
ETHICAL CONSIDERATIONS AND END-OF-LIFE CARE

In patients with end-stage disease in whom all available treatment options have been exhausted, limitations on advanced treatments should be considered and discussed with the patient and/or his relatives, when appropriate.

This may imply the decision not to admit a patient to the ICU if the prognosis is poor. In such cases, providing comfort and symptom relief may become the main objectives, as in other patients approaching the end of their lives. Novel technical developments such as ECLS may create hope but at the same time new ethical dilemmas arise. So far predominantly used as a bridge to transplantation, ECLS may also be considered a bridge to recovery in patients with treatable triggers of RV failure. Without the perspective of transplantation, however, ECLS strategies will frequently fail, which may result in complex decisions about if and when to conclude this treatment.

by mansdocs.com

Flowchart 3: Treatment guidelines for right heart failure.



Similar problems will arise when ECLS devices are being used in pregnant patients. Although this strategy may stabilize the mother for weeks or even months, thus allowing maturation of the fetus and successful delivery, there is a high likelihood that it will be impossible to wean the mother from the device, causing immense psychological problems for the patient, her family, and her caregivers.

SUMMARY

Despite advances in medical therapy, acute right heart failure remains a lethal condition for many patients. Owing to the expertise required to manage these patients, their inherent complexity, and resource requirements, these patients are best managed in experienced centers. The principles of care should focus on improving RV function and oxygen delivery to prevent the development of multiorgan failure, by optimizing preload, reducing afterload, and improving RV contractility. Preservation of coronary blood flow and avoiding treatment-induced increases in heart rate should also guide treatment decisions.

Unfortunately, there are few data to guide clinicians on the best pharmacological therapies in these patients. There is a clear need to improve our understanding of RV adaptation and develop strategies to avoid RV decompensation.

Treatment decisions therefore are based on biological plausibility and clinical experience. Extracorporeal support is currently regarded as a bridge to lung transplantation, but may one day become a destination therapy. Lung

by mansdocs.com

transplantation and pulmonary endarterectomy remain definitive destination therapies in select patients who are eligible for these surgical treatments. Patients who are not eligible for destination therapy need to be counseled in advance to ensure that discussions regarding treatment options, end-of-life decision-making, and palliative measures are instituted, when appropriate.

BIBLIOGRAPHY

1. Alaverdian A, Cohen RI. The Right Ventricle in Critical Illness. The Open Critical Care Medicine Journal. 2010;3:38-42,1874-8287.
2. Bakšyte G. Acute right ventricular failure. Acta Medica Lituanica. 2012;19(3):220-3.
3. Hoeper MH, Granton J. Concise clinical review: intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184:1114-24.
4. Lahm T, McCaslin CA, Wozniak TC, et al. Medical and surgical treatment of acute right ventricular failure. J Am Coll Cardiol. 2010;56:1435-46.
5. Granton J, Mercier O, Perrot MD. Management of Severe Pulmonary Arterial Hypertension. Semin Respir Crit Care Med. 2013;34(5):700-13.
6. Gayat E, Mebazaa A. Pulmonary hypertension in critical care. Curr Opin Crit Care. 2011;17:439-48.

by mansdocs.com

SECTION 3

Respiratory Care

by mansdocs.com

by mansdocs.com

CHAPTER

22

Community Acquired Pneumonia

Rajesh Pande, Mir Faisal Mazid

INTRODUCTION

Community Acquired Pneumonia (CAP) refers to an acute infection of the lung parenchyma acquired through contacts in the community and is manifested by fever, cough, chest pain, breathing difficulty and radiographic signs of consolidation of a part or parts of one or both lungs. It affects millions of people annually throughout the world.

Affected patients may be treated with antimicrobial therapy on an outdoor basis, but serious patients may need to be hospitalized and generally have a higher mortality. The common organisms causing community acquired pneumonia include Hemophilus influenza, *Staphylococcus aureus*, *Streptococcus pneumoniae*, Moraxella catarrhalis, and Legionella pneumophila. The diagnosis of Community Acquired Pneumonia requires knowledge of clinical features, imaging, microbiology cultures as well as laboratory tests. Following management guidelines in CAP has been shown to reduce crude 30-day mortality by 3.2%. Physicians also need to understand about the role of immunophrophylaxis in susceptible patient groups.

EPIDEMIOLOGY

Definition

CAP may be defined on the basis of clinical and radiographic findings:

- Symptoms of acute lower respiratory tract illness—cough with or without expectoration, shortness of breath, pleuritic chest pain for less than 1 week
- At least 1 systemic feature-temperature greater than 37.7°C, chills and rigors, and/or severe malaise
- New focal chest signs on examination—bronchial breath sounds and/or crackles
- When chest X-ray is available—new shadows for which there is no other explanation—not due to pulmonary edema or infarction (Fig. 1).
- No other explanation for the illness.

Incidence, Morbidity and Mortality

In the US, about 1 million episodes of CAP have been estimated to occur every year in adults older than 65 years of age. The cost of inpatient care for pneumonia is up to 25 times greater than that of outpatient care

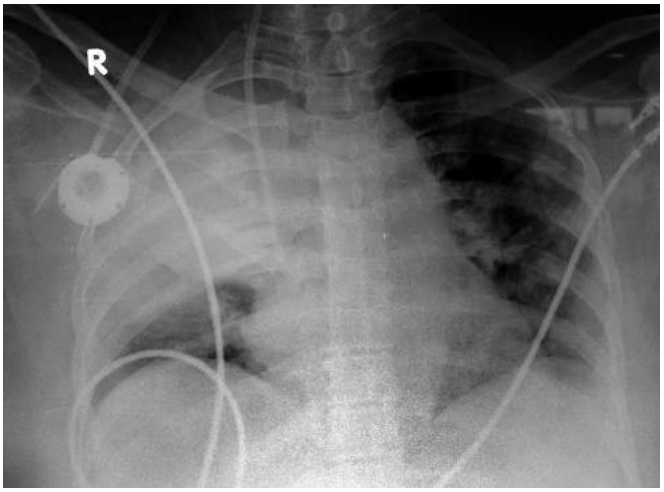


Fig. 1: Right sided community-acquired pneumonia.

by mansdocs.com

and consumes about 10 billion dollars and 45,000 deaths annually in the US. The mortality rate is less than 1% in US and Europe in patients who do not require hospitalization, but increase to 12–14% in admitted patients and 30–40% if they are admitted in ICU. As per Global Burden of Disease Study, lower respiratory infections were the most common specific cause of global disability-adjusted life-years (DALYS) and the highest disease burdens were in sub-Saharan Africa (21.4%) and India (20.9%).

Classification of Pneumonia

Lobar pneumonia: The bacterial exudation starts distally and spreads through the terminal air spaces resulting in flooding of the alveoli. Air bronchograms are a classical feature of lobar pneumonia. Pneumococcal pneumonia is the most common pneumonia to produce lobar pattern. *Klebsiella* is also a common causative organism.

Bronchopneumonia: The infections spread along the airway and finally reaches the distal areas. The radiologic pattern is poorly defined and is often patchy and may be confluent over a period of time. This pattern is produced by many organism including *Staphylococcus*, gram negative pathogens and anaerobes.

Interstitial: The predominant damage is to the bronchiolar walls and the interstitium. Linear, reticular and small nodular opacities are seen. The classic examples are viruses and mycoplasma. Viral pneumonia can mimic a lobar pneumonia.

Risk Factors Associated with CAP

Risk factors associated with Community Acquired pneumonia (Kandi S, JAPI- 2012) (Table 1).

PATHOGENESIS OF CAP

Causative Agents

In India studies have identified different organisms as the commonest organisms from a particular geographical area: *Streptococcus pneumoniae* in Shimla and Delhi, *Pseudomonas aeruginosa* in Ludhiana, whereas the common agents identified from Srinagar were *Staphylococcus aureus, E coli, Kleibseilla pneumoniae, S pyogenes* and *Acinetobacter* (Tables 2 to 4).

Atypical pneumonia: The term is used to refer to a group of organisms-*Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella, Coxiella burnetii*.

Table 1: Risk factors and organisms associated with community acquired pneumonia (CAP).

Risk factor	*Possible organisms*
Aspiration	Anaerobes and Gram negative organisms
Alcoholism and Diabetes	Pneumococcal, anaerobic and mixed infections
Immunosuppression	*Legionella*
Cigarette smoking	Invasive pneumococcal disease
COPD	*Hemophilus influenzae* and *Moraxella catarrhalis*
Nursing home residents	*Hemophilus influenzae, Mycoplasma pneumoniae and Legionella*
Health care worker	*Mycobacteria tuberculosis*
Veterinarian	*Coxiella burnetii*

Table 2: Organisms causing pneumonia in outpatients.

Patient type	*Etiology*
Outpatient	
	Streptococcus pneumoniae
	Mycoplasma pneumoniae
	Hemophilus influenzae
	Chlamydia pneumoniae
	Respiratory viruses

Table 3: Organisms causing pneumonia in inpatients (ward).

Patient type	*Etiology*
Inpatient (WARD)	
	Streptococcus pneumoniae
	Mycoplasma pneumoniae
	Hemophilus influenzae
	Chlamydia pneumoniae
	Legionella species
	Aspiration
	Respiratory viruses

Table 4: Organisms causing pneumonia in inpatients (ICU).

Patient type	*Etiology*
Inpatient (ICU)	
	Streptococcus pneumoniae
	Staphylococcus aureus
	Legionella species
	Gram negative bacilli
	Hemophilus influenzae

by mansdocs.com

Diagnosis

Clinical features: Symptoms of community acquired pneumonia include fever (90–97%), cough (88–97%), expectoration (66–87%), dyspnea (48–71%), chest pain (34–64%), chills (30%), hemoptysis (17%) and confusion (17%). Non-respiratory symptoms such as headache, nausea, vomiting, abdominal pain, diarrhea, myalgia, and arthralgia are also common in patients with pneumonia.

Elderly patients present with fewer symptoms but can present more often with confusion. Signs: Fever is usually present, but some patients may be hypothermic (a poor prognostic sign), and some (20%) are afebrile at the time of presentation with pneumonia. Crackles are heard on auscultation over the affected area of lung, and physical findings of consolidation (dullness to percussion, increased tactile, vocal fremitus, whispering pectoriloquy, and bronchial breath sounds) are present in about 20% of patients with pneumonia. A pleural friction rub is heard in about 10% of cases.

Chest X-ray: Radiographic shadow may be seen in the form of a lobar or patchy consolidation, loss of normal diaphragmatic, cardiac or mediastinal silhouette, interstitial infiltrates, or bilateral perihilar opacities, with no other obvious cause. An opacity on the chest radiograph is considered the gold standard for the diagnosis of pneumonia. However, this opacity may be due to infection, infarction, hemorrhage, edema fluid, malignancy, or inflammation caused by a variety of conditions. In about 20% of patients with symptoms compatible with pneumonia and a chest radiograph read as normal or no pneumonia by the radiologist, computed tomography (CT) of the chest will be compatible with pneumonia.

Laboratory tests:

- Chest X-ray
- Complete blood count
- *Sputum Gram stain and culture*: More than or equal to 25 WBC and 10 squamous epithelial cells per HPF suggests that it is a good sample for examination
- Blood culture
- *Blood chemistry*: Glucose, electrolytes, liver and kidney function tests
- Pulse oxymetry
- ABG
- *Serum antibodies*: *Streptococcus pneumoniae, mycoplasma, chlamydia*, adenovirus, influenza A and B viruses, parainfluenza viruses 1, 2 and 3, and respiratory syncytial virus
- *PCR*: *Mycoplasma, chlamydia pneumoniae, Haemophilus influenzae*
- *Urine antigen tests for*: *Legionella, Pneumococcus*
- Thoracocentesis if pleural effusion is significant
- *Bronchoscopy*: Bronchoalveolar lavage, protected specimen brush
- *Biomarkers*: C-reactive protein, procalcitonin.

IDSA Suggested Investigations Guidelines in CAP (Table 5)

Urine antigen for *Legionella* and *Pneumococcus* are not routinely done in uncomplicated pneumonias.

Table 5: Investigation guidelines in CAP.

Indication	*Blood culture*	*Sputum culture*	*Legionella UAT*	*Pneumococcal UAT*	*Others*
ICU admission	+	+	+	+	ET aspirate/ BAL/LRT sample
Failure of OPD antibiotic therapy		+	+		
Cavitatory infiltrates	+				Fungal/ tubercular cultures
Leukopenia	+				
Alcohol abuse	+	+	+		
CLD	+			+	
Severe obstructive/structural lung disease		+			
Aspenia	+			+	
Positive Legionella UAT result		Special media for Legionella			
Positive pneumococcal UAT positive	+	+			
Pleural effusion	+	+	+	+	Thoracocentesis and culture

by mansdocs.com

Management of CAP

Hospital admission decisions in CAP: Attempts have been made to identify moderate to high-risk patients who may require hospital or ICU admission. Two most popular scores are CURB 65 developed by the British Thoracic Society and Pneumonia Severity Index.

British Thoracic Society Criteria (BTS)-CURB 65

It includes 5 easily measurable factors as indicators of increased mortality:

- Confusion (disorientation to person, place, or time),
- BUN level greater than 7 mmol/L (20 mg/dL)
- Respiratory rate greater than or equal to 30 breaths/min
- Blood pressure (systolic <90 mm Hg; or diastolic, ≤ 60 mm Hg)
- Age more than or equal to 65 years.

The 30-day mortality among patients with CURB 65 score of 0, 1, or 2 factors was 0.7%, 2.1% and 9.2%, respectively. Mortality was higher when 3, 4, or 5 factors were present and was reported as 14.5%, 40% and 57%, respectively.

Patients with a CURB-65 score of 0–1 should be treated as outpatients. A score of 2 is admitted to the wards. Patients with a score of greater than or equal 3 often required ICU care.

Pneumonia Severity Index (PSI) (Flowchart 1 & Tables 6 and 7)

Pneumonia severity index, often known as the PORT (patient outcomes research team) score has been developed by Michael Fine and colleagues. It assigns points to each of 20 different items that had been shown to be associated with mortality in CAP. This system allows categorization of patients with pneumonia into five strata, with increasing risk for mortality from risk class I to V.

Flowchart 1: Pneumonia severity index (Step 1).

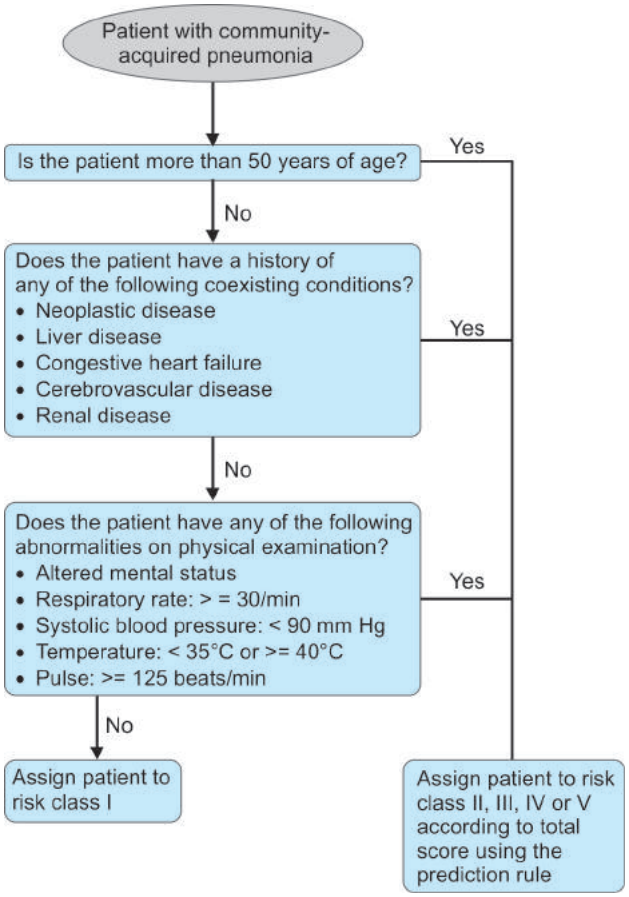


Table 6: PSI: Step 2: Score allocation in PSI.

Age (in years)	
Men	
Women	–10
Nursing home resident	+10
Coexisting illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Findings on physical examination	
Altered mental status	+20
Respiratory rate >= 30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35ºC or >= 40ºC	+15
Pulse >= 125 beats/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen >= 30/mg/dL (11 mmol/liter)	+20
Sodium < 130 mmol/liter	+20
Glucose >= 250 mg/dL (14 mmol/liter)	+10
Hematocrit <30%	+10
Partial pressure of arterial oxygen < 60 mm Hg or oxygen saturation < 90%	+10
Pleural effusion	+10

by mansdocs.com

Table 7: PSI: Step 3: Stratification of risk score.

Risk	*Risk Class*	*Score*	*Mortality*	
Low	I	Based on algorithm	0.1%	Outpatient treatment
Low	II	<= 70	0.6%	
Low	III	71–90	0.9%	
Moderate	IV	91–130	9.3%	Hospital admission
High	V	>130	27.0%	

Mortality is less than 1% for patients in risk classes I to III, but increases to 9% in class IV and to 27% in class V. Patients in risk classes I and II can usually be treated at home; those in risk class III and above may require hospitalisation.

Severe pneumonia: ATS has also given criteria to classify CAP as severe requiring ICU admission.

Criteria for Severe Community Acquired Pneumonia

Minor Criteria

- Respiratory rate greater than or equal to 30 breaths/min
- PaO_2/FiO_2 ratio of less than or equal to 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level, ≥20 mg/dL)
- Leukopenia (WBC count <4000 cells/mm^3)
- Thrombocytopenia (platelet count < 100,000 cells/mm^3)
- Hypothermia (core temperature, < 36°C)
- Hypotension requiring aggressive fluid resuscitation.

Major Criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors.

Antibiotic Therapy

Antibiotic therapy should be based on associated risk factors, suspected causative organism, the local sensitivity and resistance pattern as well as the pharmacokinetic and pharmacodynamic profile of the antibiotics besides the fact whether the organism has been identified or not.

Recommended Antibiotic Therapy for CAP

Outpatient Treatment

- Previously healthy and no use of antimicrobials within the previous 3 months
  - A macrolide (strong recommendation; level I evidence)
  - Doxycyline (weak recommendation; level III evidence)
- Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
  - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation)
  - A β-lactam plus a macrolide (strong recommendation)
- If the infection rate with macrolide resistant (MIC ≥16 μg/mL) *Streptococcus pneumoniae* is high (infection rate >25%) and patients are without comorbidities, use antibiotics listed above (moderate recommendation)
- Inpatients, non-ICU treatment
  - A respiratory fluoroquinolone (strong recommendation)
  - A β-lactam plus a macrolide (strong recommendation)
- Inpatients, ICU treatment
  - A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence) or a respiratory
  - fluoroquinolone (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).

Special Concerns

- If Pseudomonas is a consideration
  - An anti-pneumococcal, anti-pseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg) or
  - The above β-lactam plus an aminoglycoside and azithromycin or
  - The above β-lactam plus an aminoglycoside and an anti-pneumococcal
  - Fluoroquinolones (for penicillin-allergic patients, substitute aztreonam for above β-lactam) (moderate recommendation; level III evidence).
- If CA-MRSA is a consideration
  - Add vancomycin or linezolid (moderate recommendation).

by mansdocs.com

Duration of Antibiotic Therapy and Switchover to Oral Antibiotics

Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy.

A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extra-pulmonary infection, such as meningitis or endocarditis.

Parenteral antibiotics may be changed to oral preparations once clinical stability has been achieved, and the patients may be discharged.

The criteria for clinical stability are as follows:

- Temperature less than or equal to 37.8°C
- Heart rate less than or equal to 100 beats/min
- Respiratory rate less than or equal to 24 breaths/min
- Systolic blood pressure greater than or equal to 90 mm Hg
- Arterial oxygen saturation greater than or equal to 90% or pO_2 greater than or equal to 60 mm Hg on room air-Ability to maintain oral intake
- Normal mental status.

Treatment of Viral Pneumonias

For influenza A, early treatment (within 48 hours) with oseltamivir or zanamivir is recommended. Early treatment with these drugs reduces the likelihood of lower respiratory tract complications. Oseltamivir is a good choice because of its broad influenza spectrum, low risk of resistance emergence and lack of bronchospasm. However the use of these drugs is not recommended for patients with uncomplicated pneumonia with symptoms more than 48 hours. Amantadine or rimantadine should not be used for treatment or chemoprophylaxis as they are active against only influenza A virus.

No proven antiviral therapy is available for viral pneumonias like-parainfluenza virus, RSV, adenovirus, the SARS virus or hanta-virus. In all these suspected pneumonias, a high clinical suspicion of bacterial superinfection should be kept in mind.

Nonresponding Pneumonia

Most cases of CAP are treated empirically because of limitation of diagnostic testing. However 6–15% of hospitalized patients with CAP do not respond to antibiotics. Mortality in nonresponders is many folds high when compared to responders. Nonresolving pneumonia can be described as pneumonia where clinical features do not improve despite antibiotic therapy for 10 days or more.

The common causes are:

- *Pathogen related*: Resistant microorganism, Non bacterial pathogens like mycobacterium tuberculosis, atypical mycobacteria, fungal nocardia or actinomycosis.
- *Host related*: Comorbidities, severe initial illness, and immunosuppression
- *Noninfectious*: *BOOP. Misdiagnosis*: Pulmonary embolism, CHF, Vasculitis, drug fever
- *Complications*: Nosocomial superinfection, exacerbation of comorbid illness, empyema, abscess, metastatic infection-empyema/parapneumonic meningitis, endocarditis, arthritis.

These patients may require to be shifted to a tertiary centre, additional diagnostic testing and escalation or changes in treatment. CT chest, bronchoscopy and other specific diagnostic tests may aid in clinching a possible diagnosis.

Prevention

All persons more than or equal to 50 years of age, others at risk for influenza complications, household contacts of high-risk persons, and health care workers should receive inactivated influenza vaccine every year.

Pneumococcal polysaccharide vaccine is recommended at convalescence, for persons more than or equal to 65 years of age and for those with selected high-risk concurrent diseases, according to current Advisory Committee on Immunization Practices- CDC guidelines.

SUMMARY

Community acquired pneumonia is a common illness and is sometimes associated with high morbidity and mortality. One should be familiar with the causative organisms and the risk factors. It is important to diagnose pneumonia and do risk stratification, which helps in deciding about admission as well as about the choice of antibiotic therapy. Chest X-ray, blood chemistry, blood cultures and respiratory specimen cultures play a very important part in the diagnosis. CURB 65 and PSI help in clinical decision-making and are good tools. The physician is advised to go through the available Indian as well as international guidelines available on treatment of CAP.

by mansdocs.com

High-risk groups should receive prophylaxis against influenza and pneumococcus.

BIBLIOGRAPHY

1. Bansal S, Kashyap S, Pal LS, et al. Clinical and bacteriological profile of community acquired pneumonia in Shimla, Himachal Pradesh. Indian J Chest Dis Allied Sci. 2004;46: 17-22.
2. Dhar R. Pneumonia review of guidelines. J Assoc Physicians India. 2012;60 Suppl:25-8.
3. Guleria R, Kumar J. Management of community acquired pneumonia. J Assoc Physicians India. 2012;60 Suppl:21-4.
4. Gupta D, Agarwal R, Aggarwal AN, et al. Guidelines for diagnosis and management of community- and hospital acquired pneumonia in adults: Joint ICS/NCCP (I) recommendations. Lung India. 2012;29(Suppl 2):S27-62.
5. Halm EA, Teirstien AS. Clinical practice. Management of community-acquired pneumonia. N Engl J Med. 2002;347; 2039-45.
6. IDSA/ATS Consensus guidelines on the management of community acquired pneumonia in adults. Clinical Infectious Diseases 2007;44:S27-72.
7. Kandi S. Diagnosis of community acquired pneumonia. J Assoc Physicians India. 2012;60 Suppl:17-20.
8. Wattanathum A, Chaoprasong C, Nunthapisud P, et al. Community- acquired pneumonia in South East Asia: The microbial differences between ambulatory and hospitalized patients. Chest 2003;123:1512-9.

by mansdocs.com

CHAPTER

23

Ventilator-Associated Pneumonia

Manoj K Goel

INTRODUCTION

Ventilator-associated pneumonia (VAP) is pneumonia that develops 48 hours or longer after mechanical ventilation is given by means of an endotracheal tube or tracheostomy. VAP results from the invasion of the lower respiratory tract and lung parenchyma by microorganisms. Intubation compromises the integrity of the oropharynx and trachea and allows oral and gastric secretions to enter the lower airways.

Hospital-acquired pneumonia (HAP) is pneumonia that develops 48 hours or longer after admission to a hospital. HAP is the second most common nosocomial infection. HAP increases patient's hospital stay by approximately 7–9 days and can increase hospital costs by an average of $40,000 per patient.

HEALTHCARE-ASSOCIATED PNEUMONIA

Healthcare-associated pneumonia is pneumonia that occurs in persons in one of the following groups:

- Patients who have been hospitalized in an acute care facility for 2 or more days within 90 days of the infection
- Residents of a nursing home or long-term care facility
- Patients who received intravenous antibiotic therapy, chemotherapy, or wound care within the last 30 days of the current infection
- Patients who receive hemodialysis in any setting.

EPIDEMIOLOGY OF VAP

Ventilator-associated pneumonia is a complication in as many as 28% of patients who receive mechanical ventilation. The incidence of VAP increases with the duration of mechanical ventilation. Estimated rates are 3% per day for the first 5 days, 2% per day for days 6–10, and 1% per day after day 10.

The crude mortality rate for VAP is 27–76%. *Pseudomonas* or *Acinetobacter* pneumonia is associated with higher mortality rate than those associated with other organisms. Studies have consistently shown that a delay in starting appropriate and adequately dosed antibiotic therapy increases the mortality risk.

Outcomes are also related to the timing of the onset of VAP. Early-onset pneumonia occurs within the first 4 days of hospitalization, whereas late-onset VAP develops 5 or more days after admission. Late-onset pneumonias are usually associated with multidrug-resistant (MDR) organisms.

CLINICAL PRESENTATION OF VAP

Patient History

The patient's medical history should include an assessment of risk factors related to MDR pathogens. Such risk factors include the following:

- Current hospitalization of more than 5 days
- Hospital admission more than 2 days in the preceding 90 days

by mansdocs.com

- Antibiotic use in the previous 90 days
- Residence in a nursing home or extended-care facility
- Home infusion therapy and wound care
- Long-term dialysis within 30 days
- Immunocompromise.

This assessment is important so that appropriate empiric antibiotics can be initiated before bacterial culture results return. If appropriate empiric antibiotics are selected, the subsequent adjustment of antibiotics does not improve the patient's mortality risk.

Diagnostic Triad

The diagnostic triad for VAP consists of the following clinical criteria:

- Pulmonary infection: Signs include fever, purulent secretions, and leukocytosis
- Bacteriologic evidence of pulmonary infection
- Radiologic suggestion of pulmonary infection.

When the combination of radiologic infiltrates and two clinical criteria are observed, the sensitivity of diagnosing VAP is 69% and the specificity is 75%.

RISK FACTORS FOR VAP

Intubation Considerations

Intubation with mechanical ventilation increases the risk of HAP 3- to 21-fold and should be avoided if possible. Noninvasive positive-pressure ventilation is an option to consider, especially in the patients with exacerbations of chronic obstructive pulmonary disease and patients with immunosuppression and respiratory failure.

Patient Position

Patient position can be associated with an increased incidence of HAP and VAP. The incidence of HAP is increased in supine patients when compared with semirecumbent patients; although, there is no difference in mortality.

Subglottic Aspiration

Continuous aspiration of subglottic secretions reduces the risk of early-onset VAP. Results of a randomized, controlled trial showed a significant reduction in VAP (relative risk reduction of 42%), including late-onset VAP, when subglottic secretion drainage was performed while patients were on mechanical ventilation. Cuff pressure should be maintained at greater than 20 cm of water to prevent aspiration around the endotracheal tube.

Humidification

Passive humidifiers or heat moisture exchangers are preferred to reduce colonization of the ventilator circuit. Ventilatory circuit condensation should be prevented from entering the endotracheal tubes and any inline nebulizer. Frequent changes of the ventilator circuit, however, have not been shown to reduce the risk of VAP and are currently not recommended.

Sedation and Weaning

Protocols for sedation and weaning should be applied in the ICU to reduce the duration of mechanical ventilation. Over and prolonged sedation as well as failed extubation and delayed weaning are associated with increased risks of VAP.

Feeding, Aspiration, and Body Positioning

Placing patients in a semirecumbent position is associated with approximately a 3-fold reduction in the risk of HAP, especially during enteral feeding. Early enteral feeding is currently recommended. It offers a number of advantages in delivering nutrition.

Prevention of Stress-Related Bleeding

Studies comparing H_2 receptor blockers with sucralfate have shown conflicting results, with a trend toward a reduction of VAP with the use of sucralfate. These benefits are most notable with late-onset VAP. Use of sucralfate is also associated with a 4% increase in clinically significant bleeding. Proton pump inhibitors also may be used to prevent stress-related gastrointestinal bleeding.

Use of Antibiotics and Control of Colonization

Rinses with oral chlorhexidine may help prevent ICU-acquired HAP in patients. Alteration of the florae in the digestive tract due to oral or systemic antibiotics (i.e. selective decontamination of the digestive tract) effectively reduces the incidence of ICU-acquired HAP in ICUs where the levels of antibiotic resistance are low. However, routine use of this approach is not recommended.

LABORATORY STUDIES

Routine blood tests should be obtained to evaluate the patient for infection (white blood cell count) and to assess the patient's baseline renal and hepatic function for dosing of antibiotics. Blood cultures should also be obtained.

by mansdocs.com

Samples of respiratory secretions from the distal respiratory tract with either bronchoscopic or nonbronchoscopic tests should be considered. Examples of these tests are blind bronchoalveolar lavage (BAL), bronchoscopic BAL, bronchoscopy-guided protected specimen brush (PSB) sampling, and blind PSB sampling. Quantitative bacterial cultures are generally recommended to increase the reliability of these respiratory sampling techniques.

New markers such as procalcitonin and triggering receptors expressed on myeloid cells (TREM-1) are being evaluated.

IMAGING STUDIES

In the ICU, portable chest radiography is commonly used in the diagnosis of VAP. No single radiographic sign has diagnostic accuracy better than 68%. Among patients in the ICU, many infectious and noninfectious processes may cause the radiologic appearance of infiltrates. The absence of a radiologic infiltrate is helpful in excluding the diagnosis of VAP.

Chest CT scanning can be performed to evaluate the patient for underlying lung parenchyma disease, pleural effusions, and attenuation of consolidations.

Ultrasonography of the chest may be obtained to aid in the evaluation of pleural effusions and to guide sampling or drainage of the pleural fluid.

SAMPLING OF SECRETIONS IN THE PROXIMAL AIRWAY

Qualitative endotracheal aspirates are easy to obtain but have a high false-positive rate in ICU patients because of airway colonization. When quantitative endotracheal-aspirate cultures are used, a cutoff value of 10^6 is the most accurate, with a sensitivity of 38–82% and a specificity of 72–85%. However, when this cutoff is used, approximately 33% of patients with VAP may be missed. Only 40% of endotracheal-aspirate cultures coincide with results of protected brush sampling. Therefore, adjusting antibiotics on the basis of findings from endotracheal aspirates may lead to inadequate coverage of the causative pathogens.

SAMPLING OF SECRETIONS IN THE DISTAL AIRWAY

Distal airway samples may be obtained by using bronchoscopic or nonbronchoscopic techniques. With nonbronchoscopic techniques, a catheter is blindly advanced through the endotracheal tube or tracheostomy and wedged in the distal airway. Various sampling methods include blind bronchial suction (BBS), blind BAL, and blind PSB sampling. Their sensitivities and specificities, respectively are BBS—74–97% and 74–100%, blind BAL—63–100% and 66–96% and blind PSB sampling—58–96% and 71–100%.

Bronchoscopic Sampling

For bronchoscopic sampling of the distal airway, a bronchoscopist must be available. Bronchoscopy is performed, and specimens are retrieved from specific areas of the bronchial tree. Regions to be sampled are determined from imaging studies, areas of maximal bronchial abnormality, or dependent airway segments.

The techniques are usually BAL and PSB sampling. With BAL, an aliquot of at least 120–250 mL of nonbacteriostatic sodium chloride solution is introduced through the wedged bronchoscope. When BAL is adequately performed, approximately 1 million alveoli are sampled.

As with any sampling procedure, proper technique is imperative to obtain reliable results. Because contamination from the oropharynx inevitably occurs during BAL, quantitative thresholds of less than 10^4 colony-forming units (cfu)/mL are generally considered contaminants, whereas those in the range of 10^5–10^6 cfu are considered true pathogens.

With the bronchoscopic PSB method, the distal airway is sampled by telescoping the brush out of a sheath with a protective cap. When adequately performed, the sensitivity and specificity of bronchoscopic PSB sampling are approximately 89% and 94%, respectively. Because the clinician can retrieve 0.001–0.01 mL secretions (diluted in 1 mL of sodium chloride solution), a threshold of 10^3 represents a sample of 10^5–10^6 cfu/mL.

Sensitivities and specificities of bronchoscopic BAL and PSB sampling, respectively, are BAL—42–93% and 45–100% and PSB sampling—33–100% and 50–100%.

THORACOCENTESIS, THORACOTOMY, AND BIOPSY

Thoracentesis may be indicated to determine whether or not the pleural space is infected. Additionally, when the etiology of the pulmonary infiltrates remains unclear, procedures such as video-assisted thoracotomy or an open lung biopsy may be required to establish a diagnosis.

by mansdocs.com

TREATMENT OF NOSOCOMIAL PNEUMONIA

Patients with severe HAP or health care–acquired pneumonia who require mechanical ventilatory support should be treated in a fashion similar to that of patients with VAP.

Ventilator-associated tracheobronchitis (VAT) is an intermediate condition between airway colonization and VAP. A study of ICU patients found that, although, VAT is less common than VAP, it had a similar incidence and frequently progressed to VAP. Patients diagnosed with VAT had similar outcomes to those with VAP, meaning antimicrobial therapy is appropriate.

Selection of Antibiotics

For patients with early-onset VAP and no risk factors for MDR pathogens, currently recommended initial empiric antibiotics include one of the following options: ceftriaxone, fluoroquinolones, ampicillin-sulbactam or ertapenem.

For patients with VAP and risk factors for MDR pathogens or for patients with late-onset VAP, initial antibiotic therapy may consist of one of the following options:

- Antipseudomonal cephalosporins (e.g. cefepime or ceftazidime)
- Antipseudomonal carbapenems (imipenem or meropenem)
- Beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam) with an antipseudomonal fluoroquinolone (ciprofloxacin) or aminoglycoside plus linezolid or vancomycin(if risk factors for methicillin-resistant *Staphylococcus aureus* are present).

If infection with *Legionella pneumophila* is suspected, the regimen should include a macrolide or fluoroquinolone rather than an aminoglycoside.

Outcomes after VAP improve with the early administration of appropriate antibiotic regimens and with adequate dosing of antibiotics.

Antibiotics should be further adjusted on the basis of culture results. The first antibiotic regimen should be optimized, because inappropriate initial therapy is associated with worsened outcomes, even if the regimen is subsequently changed on the basis of the microbiologic results.

The 10 clinical caveats in selecting an empiric antibiotic regimen are as follows:

1. The administration of antibiotics should not be delayed for the sole purpose of performing diagnostic tests.
2. The empiric choice of antibiotic should be based on the patient's risk for having MDR pathogens.
3. Combination therapies are preferred as the initial regimens in patients at risk for infection with MDR pathogens to avoid inappropriate antibiotics.
4. Local antibiograms should be reviewed when empiric therapy is being selected.
5. If the patient received antibiotics in the recent past, the new antibiotic should be chosen from a class different from the previous ones to avoid selecting antibiotics to which the bacterial pathogen has become resistant.
6. When an appropriate and adequate initial antibiotic regimen is started, every effort should be made to shorten the duration of antibiotic therapy. If a patient receives appropriate and adequate empiric antibiotic therapy, the duration of antibiotic treatment may be shortened from the traditional 14–21 days to 7 days if the etiologic organism is not *Pseudomonas aeruginosa*.
7. False-negative culture results occur in patients who have been taking antibiotics for 24–72 hours before the collection of respiratory specimens. In these patients, using a BAL threshold 10-fold lower than usual may be helpful for avoiding false-negative results.
8. If the clinical pretest probability for VAP is high, antibiotics should be started promptly regardless of whether the culture results are positive.
9. Aerosolized antibiotics may be used as an adjunct to systemic antibiotics; although, they have not been shown to be effective as sole therapy for VAP.
10. Certain organisms, such as *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species produce extended-spectrum beta-lactamase (ESBL), and screening tests for the production of ESBL should be performed. Carbapenems are generally effective against these ESBL-producing organisms.

Antibiotic selection in trauma is similar. The prevalence of early VAP (defined as = 4d) due to MRSA in patients with multiorgan trauma is low even in communities with a high incidence of community-acquired MRSA. Thus, coverage for MRSA in early VAP in a patient with multiorgan trauma is not necessary unless the patient has identified risk factors. Patients with multiorgan trauma who develop late VAP (defined as > 4d) are at a higher risk for MSRA pneumonia and should be treated accordingly. Antibiotics can be de-escalated based on culture results.

by mansdocs.com

Patterns of Antibiotic Resistance

Clinicians should be aware of the local antibiotic resistance pattern in order to adequately begin an empiric antibiotic regimen. Other important factors are an adequate dose, the route of administration, and an understanding of the pharmacodynamic properties of particular antibiotics.

Beta-lactam antibiotics achieve less than 50% of the serum concentration in the lung, whereas fluoroquinolones and linezolid are found in comparable concentrations in bronchial secretions.

Aminoglycosides and quinolones are bactericidal in a concentration-dependent manner. In comparison, agents such as vancomycin and beta-lactams are bactericidal in a time-dependent fashion; that is, their bactericidal activity depends on the time the serum concentration is above the minimal inhibitory concentration for the target organism.

BIBLIOGRAPHY

1. Campbell GD. Blinded invasive diagnostic procedures in ventilator-associated pneumonia. Chest. 2000;117 (4 Suppl 2):207S-11.
2. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002;165(7):867-903.
3. Melsen WG, Rovers MM, Bonten MJ. Ventilator-associated pneumonia and mortality: a systematic review of observational studies. Crit Care Med. 2009;37(10):2709-18.
4. Torres A, El-Ebiary M. Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia. Chest. 2000;117 (4 Suppl 2):198S-202S.

by mansdocs.com

CHAPTER

24

Acute Respiratory Distress Syndrome

Rajesh Pande, Vipin Kauts

INTRODUCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent a significant public health issue. About 150,000 people in the United States have ALI or ARDS every year and the mortality rate is between 30% and 50%. About 10–15% of ICU and 20% of ventilated patients in the ICU meet ARDS criteria. It has been seen that pulmonary function in most survivors returns nearly to normal within 6–12 months. Studies have identified various risk factors that are associated with the development of ARDS (Table 1).

Table 1: Risk factors predictive of mortality in acute respiratory distress syndrome (ARDS).

- Liver dysfunction/cirrhosis
- Sepsis
- Non-pulmonary organ dysfunction
- Age
- Organ transplantation
- HIV infection
- Active malignancy
- Length of MV prior to ARDS
- Oxygenation index (MAP × FiO_2 × 100/PaO_2)
- RV dysfunction
- PaO_2/FiO_2 <100
- Chronic alcoholism

(HIV: Human immunodeficiency virus; MV: Mechanical ventilation; MAP: Mean airway pressure; FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of oxygen in arterial blood; RV: Right ventricular).

DEFINITIONS OF ARDS

The earlier North American European Consensus Conference Definition, which are given below have been revised.

- *Onset*: Acute and persistent (Limitation-No definition of acute)
- *Oxygenation criteria*: Partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) < 300 for ALI, PaO_2/FiO_2 < 200 for ARDS (Limitation: ALI confused as P/F between 201 and 300; PEEP is not taken into consideration)
- *Exclusion criteria*: Pulmonary artery occlusion pressure (PAOP) 18 mm Hg, clinical evidence of left atrial hypertension (LAH) (Limitation: poor interobserver interpretation of PAOP and lack of definite criteria for LAH)
- *Radiographic criteria*: Bilateral opacities consistent with pulmonary edema (Limitation: poor interobserver interpretation).

Revised Berlin Definition (New consensus definitions):

This definition had some limitations. It did not define acuteness of illness, did not elaborate on interpretation of chest X-ray findings. The exclusion criteria was based on PAOP, which is rarely used in clinical practice and it did not take into consideration the application PEEP/CPAP.

Therefore, new ARDS definition, called the Berlin definition were developed.

- *Timing*: Within 1 week of a known clinical insult or new or worsening respiratory symptoms
- *Chest imaging*: Bilateral opacities—not fully explained by effusions, lobar/lung collapse or nodules

by mansdocs.com

- *Origin of edema*: Respiratory failure not fully explained by cardiac or fluid overload. Need objective assessment to exclude hydrostatic edema; echocardiography if no risk factors present.
- *Oxygenation*:
  - *Mild*: 200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O.
  - *Moderate*: 100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O.
  - *Severe*: PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O.

CLINICAL DISORDERS ASSOCIATED WITH ARDS

Clinical disorders associated with ARDS:

- Direct (pulmonary ARDS)
  - Common
    - Aspiration pneumonia
    - Pneumonia
  - Less common
    - Inhalation injury
    - Pulmonary contusion
    - Fat emboli
    - Near drowning
    - Reperfusion injury
- Indirect (extrapulmonary ARDS)
  - Common
    - Sepsis
    - Severe trauma with prolonged hypotension and/or multiple fractures
    - Multiple transfusion of blood products
  - Less common
    - Acute pancreatitis
    - Cardiopulmonary bypass (CPB)
    - Drug overdose
    - Disseminated intravascular coagulation (DIC)
    - Burns
    - Head injury.

PATHOPHYSIOLOGY

Direct injury: Pulmonary epithelial cells affected by direct insult lead to inflammation causing intra-alveolar damage, alveolar filling (pulmonary consolidation). Positive end-expiratory pressure may not have major effect on opacities.

Indirect injury: The indirect insult to capillary endothelial cells causes inflammation leading to increased permeability of endothelial barrier, microvascular damage and interstitial edema. As the intra-alveolar spaces are relatively spared, PEEP produces better results (Fig. 1).

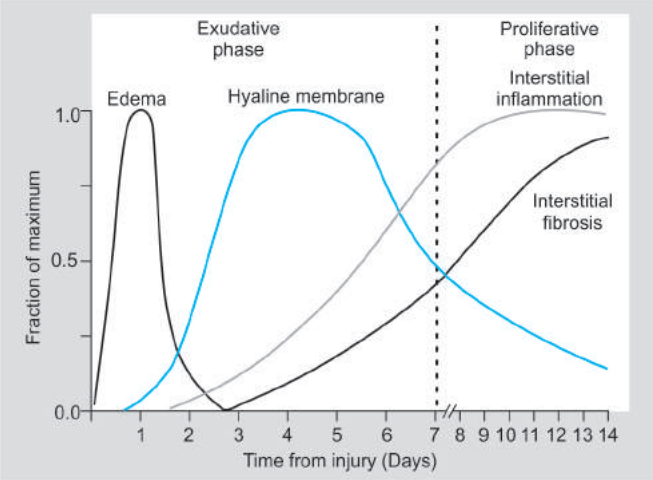


Fig. 1: Phases of acute respiratory distress syndrome.

The Acute or Exudative Phase

There is rapid onset of respiratory failure and refractory arterial hypoxemia. The chest X-ray (CXR) findings may be indistinguishable from cardiogenic pulmonary edema (CPE), asymmetric or patchy bilateral infiltrates with or without pleural effusion. Computed tomography (CT) scan shows alveolar filling, consolidation, and atelectasis predominantly in dependent lung zones with relative sparing of other areas. Bronchoalveolar lavage (BAL) may show that even the spared areas have substantial inflammation. There is neutrophil exudate to begin with followed by monocyte and lymphocyte recruitment, further aggravating the epithelial and endothelial injury. There is complex interplay of pro- and anti-inflammatory mediators and neutrophil markers in ARDS.

Intermediate Phase

After 1 week of initial insult, the type I cells start dying, type II cells become dysfunctional, unable to produce surfactant and handle sodium transport, leading to lung edema. This leads to movement of plasma cell transfer from capillaries to the lung, exposing the basement membrane to the platelets leading to intravascular coagulation causing further compromise of the lung function.

Resolution

Acute lung injury and ARDS may resolve completely from acute exudative phase. But in some after 2 weeks, it progresses to fibrosing alveolitis, which manifests as: persistent hypoxemia, increased alveolar dead space, decrease in lung compliance, severe pulmonary hypertension leading to right ventricular failure (RVF). The CXR may show linear

by mansdocs.com

opacities, consistent with the presence of evolving fibrosis, with or without pneumothorax. CT scan shows diffuse interstitial opacities and bullae. Interstitial fibroblasts differentiate into myofibroblasts and migrate into alveolar clots, initiating a fibroproliferative response, leading to a fibrous lung. This phase is associated with resorption of edema, widespread fibrosis, microvascular destruction and development of emphysema like lesions in the lung parenchyma. Rising portial pressure of carbon dioxide in arterial blood ($PaCO_2$) at a constant minute ventilation may be indicative of development of emphysema like lesions.

Baby Lung Concept

Computed tomography scan studies have shown that opacities are primarily distributed in dependent lung regions. The non-dependent lung regions are normally inflated. The intermediate zone is poorly inflated. The lung weight increases from 1,000–1,200 g to 2,000–4,000 g. The amount of residual, normally inflatable lung volume is like lung volume of a 5–6-year-old child.

Characteristics of a Baby Lung

The inflatable lung is small with a normal/near normal compliance. The normal/near normal lung located to non-dependent lung regions is associated with variable amount of abnormal lung: poorly inflated/collapsed or consolidated.

In fact, ARDS consists of three zones: (1) *baby lung,* (2) *recruitable lung and* (3) *a consolidated lung*. However, the baby lung concept does not hold true when ARDS patients aremade prone because the opacities clear in dorsal region and develop in ventral region.

EFFECT OF POSITIVE PRESSURE VENTILATION IN ARDS LUNGS

The delivered tidal volume causes alveolar inflation and recruitment of previously non-inflated areas. Pressure required is more than the pressure required to keep them open. Lung recruitment is an inspiratory phenomenon.

The next important consideration is to keep the lung open once it has been recruited. This is achieved by applying PEEP, which keeps alveoli open at end exhalation. PEEP is a compromise between lung stretching and lung recruitment and in fact the optimum PEEP does not exist. Ability to recruitment by PEEP is limited in late phase of ARDS and in primary ARDS as compression atelectasis is much less prevalent.

The ARDS lungs have a decrease in lung volume with impaired respiratory mechanics and heterogeneous distribution of loss of aeration. The airway pressures are very high and when we try to ventilate these lungs, ventilator-induced lung injury can occur, causing further deterioration in the condition (*Barotrauma*). Excessive pulmonary stretch caused by either very high peak airway pressures or large volumes causes *volutrauma* and repetitive opening and collapse of lung units during ventilation may cause *atelectrauma*. Slutsky has coined another term *biotrauma*, which reflects the inflammatory cascade enhanced by repetitive opening and closing of the alveolar units. These physical forces cause release of intracellular mediators. Some mediators directly cause lung injury, others lead to development of pulmonary fibrosis. The translocation of mediators, bacteria, or lipopolysaccharide from the airspaces into the systemic circulation may occur in ARDS lungs (increased alveolar–capillary permeability), which is induced by volutrauma or epithelial microtears.

Biological alteration cause increased concentrations of hydroxyproline, transforming growth factor β, interleukin (IL) 8, release of tumor necrosis factor alpha (TNFa), β catenin, IL-6 and IL-1β. There may be recruitment of pulmonary alveolar macrophages and neutrophils as well as activation of epithelium and endothelium resulting in physiological abnormalities like increased physiological dead space, decreased compliance, decreased PaO_2 and increased $PaCO_2$. The systemic effects due to translocation of lipopolysaccharides, bacteria and various mediators lead to increased apoptosis by multiple mechanisms causing multiorgan failure and finally death.

VENTILATORY STRATEGIES IN ARDS

The objectives are to stop derecruitment of recruited alveoli known as open lung, thus avoiding "shear stress"/atelectrauma. Various methods have been used: titrated PEEP, open lung (Amato), incremental increase in PEEP or decremental steps of PEEP, using FiO_2-PEEP table of ARDSnet or CT scan (Gattinoni).

Open Lung

It is a protective strategy where there is little or no atelectasis and an optimal gas exchange. Emphasis is on establishing and maintaining patency of all recruitable airspaces during respiratory cycle. Amato had shown that the protective strategy was associated with improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in patients with ARDS when compared with conventional ventilation.

by mansdocs.com

Table 2: Summary of ventilation procedures in ARDS net study.

Variable	*Traditional tidal volume*	*Lower tidal volume*
Ventilation mode	Volume assist-control	Volume assist-control
Initial tidal volume (based on mL/kg of predictive body weight)	12	6
Plateau pressure (cm H_2O)	≤ 50	≤30
Ventilatory rate (breaths/min) (to achieve a pH 7.3–7.45)	6–35	6–35
I:E ratio	1:1–1:3	1:1–1:3
Oxygenation goal	PaO_2, 55–80 mm Hg or SpO_2, 88–95%	PaO_2, 55–80 mm Hg or SpO_2, 88–95%
Allowable combinations of PEEP and FiO_2	0.3 and 5	0.3 and 5
	0.4 and 5	0.4 and 5
	0.4 and 8	0.4 and 8
	0.5 and 8	0.5 and 8
	0.5 and 10	0.5 and 10
	0.6 and 10	0.6 and 10
	0.7 and 10	0.7 and 10
	0.7 and 12	0.7 and 12
	0.7 and 14	0.7 and 14
	0.8 and 14	0.8 and 14
	0.9 and 14	0.9 and 14
	0.9 and 16	0.9 and 16
	0.9 and 18	0.9 and 18
	1.0 and 18	1.0 and 18
	1.0 and 20	1.0 and 20
	1.0 and 22	1.0 and 22
	1.0 and 24	1.0 and 24
Weaning	By pressure support when FiO_2<0.4	By pressure support when FiO_2<0.4

(I:E: Ratio, ratio of the duration of inspiration to the duration of expiration; PaO_2: Partial pressure of oxygen in arterial blood; SpO_2: Oxyhemoglobin saturation measured by pulse oximetry; PEEP: Positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen).

Landmark ARDS net Study

It was hypothesized that in patients with ALI/ARDS, ventilation with reduced tidal volume will limit "volutrauma" and improve survival. This was called "*lung-protective strategy*". The patients with ALI/ARDS (NAECC definitions) of less than 36 hours were ventilated with volume-assist control mode of ventilation (Table 2). The patients were randomized to receive either a tidal volume of 6 mL versus 12 mL/kg of predicted body weight (PBW) (PBW/Measured body weight = 0.83), plateau pressure ≤ 30 versus ≤ 50 cm H_2O. The ventilator rate setting was 6–35 (breaths/min) to achieve a pH goal of 7.3 to 7.45. I/E ratio varied from 1.1 to 1.3. The oxygenation goal was a PaO_2 55–80 mm Hg and oxyhemoglobin saturation measured by pulse oximetry (SpO_2) 88–95%.

A FiO_2–PEEP titration table was used:

FiO_2 0.3, 0.4, 0.4, 0.5, 0.5, 0.6, 0.7, 0.7, 0.7, 0.8, 0.9, 0.9, 0.9, 1.0, 1.0, 1.0, 1.0

PEEP 5, 5, 8, 8, 10, 10, 10, 12, 14, 14, 14, 16, 18, 18, 20, 22, 24

The trial was stopped early after the fourth interim analysis (n = 861 for efficacy; p = 0.005 for the difference in mortality between groups). The study showed that in ALI

by mansdocs.com

and ARDS patients, 6 mL/kg PBW tidal volume ventilation strategy was associated with about 9% mortality reduction, less organ failures and lower blood IL-6 and IL-8 levels. Since then this strategy has become the benchmark to ventilate the ARDS patients.

High versus Low PEEP

The same group looked at the effect of high PEEP in ARDS patients. They hypothesized that in patients with ALI/ARDS (NAECC definitions) of less than 36 hours who receive mechanical ventilation with a V_T (tidal volume) of 6 mL/kg of PBW, higher PEEP may improve clinical outcomes.

Ventilator Procedures

- Volume-assist-control mode
- *Tidal-volume goal*: 6 mL/kg of PBW
- Plateau pressure ≤30 cm H_2O
- Ventilator rate setting 6–35 (breaths/min) to achieve a pH goal of 7.3 if possible
- *I/E ratio*: 1.1 to 1.3
- *Oxygenation goal*: PaO_2 55–80 mm Hg/SpO_2 88–95%
- Allowable combination of FiO_2 and PEEP.

Low PEEP Group:

FiO_2 0.3, 0.4, 0.4, 0.5, 0.5, 0.6, 0.7, 0.7, 0.7, 0.8, 0.9, 0.9, 0.9, 1.0

PEEP 5, 5, 8 8, 10, 10, 10, 12, 14, 14, 14, 16, 18, 18-24

High PEEP Group:

FiO_2 0.3, 0.3, 0.4, 0.4, 0.5, 0.5, 0.5-0.8 ,0.8, 0.9, 1.0

PEEP 12, 14, 14, 16, 16, 18, 20, 22, 22, 22-24

The trial was stopped early after the second interim analysis (n = 549) on the basis of the specified futility-stopping rule. The study did not show any beneficial effect of higher PEEP on survival in ARDS patients.

It is difficult to predict how much PEEP the ARDS lungs would tolerate safely and Rouby has suggested that in lungs with focal loss of aeration on X-ray or CT scan, PEEP should be limited to 12 cm H_2O, whereas in lungs with diffuse loss of aeration, a higher PEEP (15-25 cm H_2O) can be used.

The use of pulmonary artery catheter (PAC) to guide the treatment of ARDS did not find any improvement in survival or organ function associated with PAC-guided therapy and in fact it was associated with more complications than central venous catheter (CVC)-guided therapy. Literature supports the use of a conservative strategy of fluid management in patients with ALI. Conservative fluid-management protocol (with a lower CVP or PAOP target) has been found to be associated with a major reduction in net fluid balance without an increase in adverse events, as compared with a liberal fluid management protocol targeting higher intravascular filling pressures. Although there was no difference in the mortality between two approaches, the conservative strategy improved lung function and decreased the duration of mechanical ventilation and ICU, without increasing non-pulmonary organ failures.

There has been controversy regarding the use of corticosteroids in ARDS.

A multicenter, randomized controlled trial of corticosteroids in patients with persistent ARDS showed that methylprednisolone was associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. The study results did not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. It concluded that starting methylprednisolone therapy more than 2 weeks after the onset of ARDS may increase the risk of death.

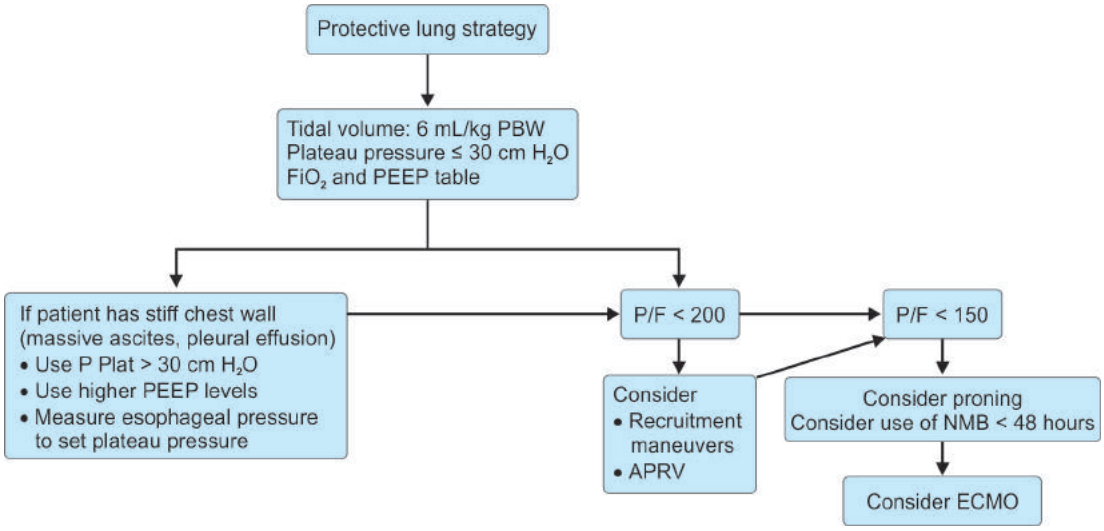
A recent French randomized clinical trial of continuous infusions of cisatracurium in patients with early ARDS and a PaO_2/FiO_2 of less than 150 mm Hg showed improved adjusted survival rates and more organ failure-free days without an increased risk in ICU acquired weakness compared with placebo-treated patients possibly due to better ventilator patient synchrony.

High frequency ventilation has gone out of favor due to two recent trials which showed no benefit and an increase in mortality with the use of high-frequency oscillatory ventilation (HFOV) in ARDS patients. Ventilation in the prone position has been documented to induce an increase in both end-expiratory lung volume and alveolar recruitment. Prone ventilation in recent studies has been found to be associated with significantly reduced overall mortality in patients with severe ARDS. A minimum of 16 hours of proning has been shown to be significantly associated with a reduction in overall mortality, although there is significant increase in pressure ulcers and major airway problems.

Although there has been significant progress in our under-standing of ARDS, the management of severe ARDS continues to be challenging with a high mortality (Flowchart 1).

by mansdocs.com

Flowchart 1: ARDS management algorithm.



(PBW: Predicted body weight; FiO_2: Fraction of inspired oxygen; Pplat: Plateau pressure; PEEP: Positive end-expiratory pressure; APRV: Airway pressure release ventilation; NMB: Neuromuscular blockade; ECMO: Extracorporeal membrane oxygenation).

BIBLIOGRAPHY

1. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. New Engl J Med. 2004;351:327-36.
2. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. New Engl J Med. 2000;342:1301-8.
3. Ware LB, Matthay MA. The acute respiratory distress syndrome. New Engl J Med. 2000;342:1334-49.

by mansdocs.com

SECTION 4

Liver and Digestive System

by mansdocs.com

by mansdocs.com

CHAPTER

25

Acute Liver Failure

Utpal Sarma, Vaibhav Kumar Nasa, Amit Kumar Singhal

INTRODUCTION

Acute liver failure (ALF) is a rare dynamic condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in individuals without known pre existing liver disease. ALF often affects young persons and carries a high morbidity and mortality. Prior to transplantation, most series suggested less than 15% survival. The potential for multiorgan failure makes ALF an extremely challenging disease to manage. In the most severe cases emergency liver transplantation is the only option. The intensive care unit (ICU) has a pivotal role in the management of this condition by providing support for failing organs while allowing time for hepatic regeneration or for preoptimization prior to liver transplantation. With better understanding of the cause, disease processes and good ICU care survival rate have been increased.

DEFINITION

Acute liver failure is defined as early as in 1970 as the development of impaired hepatic synthetic function with coagulopathy and the development of hepatic encephalopathy in the absence of underlying liver disease in less than 2–3 months. However, patients with Wilson disease, vertically-acquired hepatitis B virus (HBV), or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has only been recognized for less than 26 weeks.

"Acute liver failure" is a better overall term that should encompass all durations up to 26 weeks. There are multiple classifications of ALF. The most widely used classification of ALF is based on the speed of onset of onset of encephalopathy from when the patient becomes symptomatic. These definitions have prognostic implications and can provide clues regarding potential etiology.

Hyperacute (onset of encephalopathy 0–7 days): In the United Kingdom hyper acute presentations are almost exclusively related to paracetamol toxicity, although contributing stimuli such as ischemic insults, viral pathogens and toxins have been identified. Hyperacute group has the highest rates of spontaneous recovery.

Acute (onset of encephalopathy 7–28 days): This type of presentation is commonly seen with viral etiologies (e.g. Hepatitis B). It is associated with a moderate spontaneous survival rate but a slightly higher rate of transplantation when compared to hyperacute presentations.

Subacute (onset of encephalopathy > 28 days): A protracted course of ALF is associated with a significantly higher mortality and the etiology is often more frequently non-paracetamol drug-related. This type of presentation is difficult to distinguish from acute on chronic failure. The history and investigation play a crucial role in differentiating between the two conditions.

Bernuau and colleagues divide ALF into fulminant and subfulminant categories dependent on the jaundice to encephalopathy interval. However in young children, clinical encephalopathy can be absent or late in the course of illness, thus the definition does not depend on this symptom but only on coagulopathy due to liver injury. ALF is a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs with hepatocellular necrosis in a patient with no reported underlying chronic liver disease.

by mansdocs.com

Etiology

The specific etiology of ALF is the most important determinant of outcome. Etiology of ALF has a geographic heterogeneity. Drug-induced liver damage including acetaminophen predominates in Europe and North America whereas viral hepatitis predominating in developing countries. Other identifiable causes for ALF are Amanita phalloides, Budd-Chiari syndrome, acute fatty liver of pregnancy (AFLP), HELLP Syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) autoimmune hepatitis and Wilson's disease. Malignant infiltration of the liver is a rare but notable cause of ALF, and most often happens in elderly people.

Viral Infections

In the developing world, viral causes predominate, with infection by hepatitis A, B and E viruses accounting for most cases. Viral Hepatitis A, B and E are associated more often with acute liver injury with spontaneous recovery. However, a small percent of patients who have each of these infections will develop ALF. Hepatitis A virus is transmitted via the fecal–oral route, either through personal contact or consumption of contaminated food or water, with high incidence of infection closely associated with poor hygiene and sanitation. Viral infection follows a more severe course in adults. In children, asymptomatic infection is common. Case fatality rates rise with advanced age. ALF that is induced by hepatitis A virus most often follows a hyperacute or acute clinical course, although in elderly patients a more subacute pattern of disease can occur, which is often associated with a worse outcome.

Similar to type A, hepatitis E virus is transmitted via the fecal–oral route and is endemic throughout tropical and subtropical countries, with periodic epidemics that are mostly caused by contaminated water supply. Hepatitis E is now the most common cause of ALF in India, Pakistan, China and Southeast Asia. Hepatitis E infection is common in pregnant women, particularly in the third trimester. Vertical transmission of hepatitis E from women with acute infection results in ALF is more than half of neonates. Hepatitis E viral infection typically results in a hyperacute pattern of liver failure, although the course can also be indolent. Although overall outcomes for liver failure related to hepatitis E can be good, mortality can exceed 50% when emergency liver transplantation is unavailable.

Hepatitis B is transmitted vertically or horizontally by exposure to blood or other body fluids of an infected person. The disease accounts for nearly 30% of ALF in parts of Europe. Fewer than 4% of cases of acute hepatitis B viral infection will lead to development of the ALF, but mortality is higher than that with hepatitis A or E infections. ALF associated with hepatitis B can result not only from novel acute infection but also in chronic infection when viral status changes. These state changes include seroconversion with transition from a phase of stable viral replication or inactive carriage to viral clearance, superinfection with hepatitis D virus (HDV), or after a replication surge or reactivation. Reactivation can arise spontaneously, but more commonly happens during or after treatment-induced immunosuppression for solid-organ or hematological malignant disease. Virus reactivation is associated with a much higher risk of progression to liver failure and death than is novel acute infection. Patients at risk should be identified and antiviral prophylaxis should be initiated. High viral load at baseline is the most important risk factor for HBV reactivation. Patients with baseline HBV DNA less than 2,000 IU/mL level should continue treatment for 6 month after completion of chemotherapy or immunosuppressive therapy. Acute HBV may be more severe if there is coinfection or superinfection with HDV.

Some well-documented viral causes of ALF include herpes simplex virus types 1 and 2, human herpes virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B. Acute hepatitis C infection is very rarely implicated as a cause in Europe and the United States of America (USA), although cases have been reported in Japan and India.

Drug-induced Injury

Drug-induced injury is the second main cause of ALF and predominates in much of the developed world. In the USA and northern Europe, nonprescription paracetamol (acetaminophen) is the analgesic that is most commonly consumed in overdose, either inadvertently or with intent for deliberate self-harm. Paracetamol-induced hepatoxicity is the characteristic hyperacute form of ALF. The clinical course is often rapidly progressive multiorgan failure, with a greater severity of illness than that seen in liver failure from other causes. In the USA, paracetamol is the most common cause of ALF and incidence seems to be increasing. Toxic dose of acetaminophen that leads to ALF exceed 10 g/day (150 mg/kg). However, sustained consumption of paracetamol at therapeutic doses

by mansdocs.com

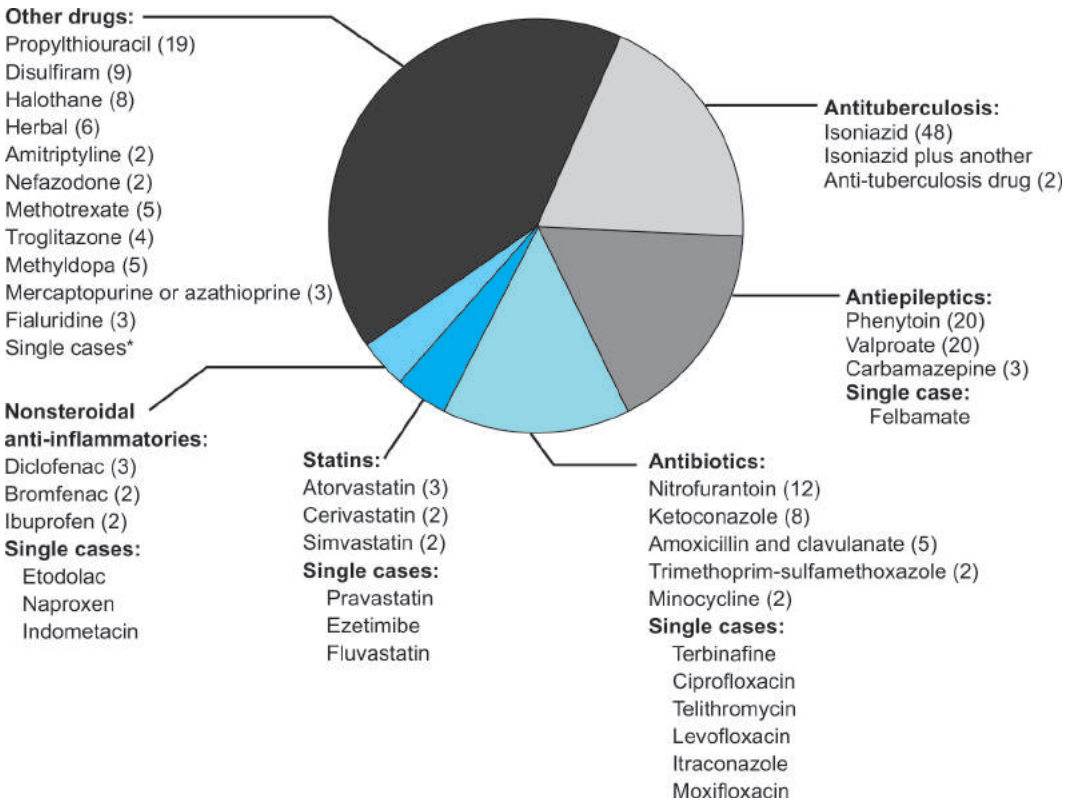


Fig. 1: Nonparacetamol-based drugs causing acute liver failure in patients requiring emergency liver transplantation in USA, 1987–2006. *Source*: Data from Mindikoglu et al. Number of cases is shown in parenthesis. *Single cases noted with sertraline, cyclobenzaprine, paroxetine, bupropion, tamoxifen, asparaginase, dactinomycin, unknown antineoplastic agents, iron, nicotinic acid, infliximab, pemoline, carbon tetrachloride, sulfasalazine, zafirlukast, loratadine, clonazepam, dapsone, diltiazem, isoflurane, labetolol, butorphanol, steroids, angiotension converting enzyme inhibitor, efavirenz, nevirapine-lamivudine, valsartan, retinol, lisinopril, allopurinol and terbinafine.

(4 g daily) can lead to asymptomatic increases of blood hepatic aminotransferase concentrations after more than 4 days of consumption.

There are various risk factors that increase the probability of acute liver damage at therapeutic dose acetaminophen such as alcoholic addiction, malnutrition, concomitant use hepatotoxic drugs.

Severe drug-induced (Fig. 1) liver injury may occur with some commonly used drugs like isoniazid, ketoconazole, disulfiram, valproate and amiodarone. Other toxic injuries, one excellent example being halothane, may trigger severe immune-mediated liver injury upon re-exposure.

Pathogenesis of Acute Liver Failure

The specific pathogenesis of the liver injury varies with the etiology. However common to all etiology is that injury to hepatocytes causes cell damage or cell death by necrosis or apoptosis. Triggering of the mitochondrial permeability transition by injury typically is associated with apoptosis if adenosine triphosphate (ATP) stores are preserved and necrosis if there is ATP depletion. Examples of mitochondrial injury associated with apoptosis include acute Wilson disease and Reye's syndrome. In the early phase of injury from warm and cold ischemia, hepatocytes and endothelial cells activate the mitochondrial permeability transition, and mitochondrial injury results in ATP depletion and ensuing necrosis. Necrotic injury of liver cells leads to a loss of cell membrane integrity and eventual rupture and cell death with the release of cytosolic proteins including lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and ferritin. Cellular glutathione is diminished, especially following ALF with acetaminophen. This increases cellular susceptibility to oxidative injury and impairs the ability to conjugate and detoxify some toxic substances. Other detoxification mechanisms are impaired, including the transport

by mansdocs.com

systems for bilirubin, leading cholestasis and conjugated hyperbilirubinemia. An important feature of acute and chronic liver injury is the general loss of Kuppfer cell function that results in reduced clearance of endotoxin and other substrates regularly presented to hepatocytes by means of the portal system, increasing the risk of infection. The site of injury within the liver plays an important role in determining the ability of the liver to regenerate. Arterial blood and portal blood rich in oxygen and nutrients are supplied in the portal tract where the liver progenitor cells, ductal hepatocytes, or oval cells are present. Injury to the portal zone inhibits the regenerative response, while injury to the central zone with sparing of the portal zone permits more frequent spontaneous recovery. The central zone is more susceptible to ischemic injury. Other toxic injuries may differ in their site of action because of differences in the metabolism of central hepatocytes compared with portal hepatocytes.

Clinical Management

Acute liver failure leads to a unique combination of often rapidly progressive, severe multiorgan failure with unpredictable complications. Emergency liver transplantation is the only effective treatment with advanced ALF. However, the general principles of care are straightforward management of ALF includes:

- Early identification, removal or amelioration of the insult that caused hepatic injury
- Organ-system support is used to improve the patient's condition to achieve maximum hepatic regeneration
- Standard ICU care
- Frequent assessment of patient.

Initial Evaluation and Case Specific Management

All patients with clinical or laboratory evidence of acute hepatitis with altered mentation should have immediate measurement of prothrombin time. Diagnosis of ALF is established with coagulopathy (INR > 1.5) associated with altered sensorium. Once diagnosis of ALF is established, patient should be admitted in ICU. The first phase of the evaluation includes obtaining a detailed history from the patient if possible or from others who may know the patient's medical history and laboratory analysis. History taking should include careful review of possible exposures to viral infection and drugs or other toxins. Physical examination should assess the patient's mental status, evaluate if there is any features of chronic liver disease.

Table 1: Grades of hepatic encephalopathy.

Grade	*Definition*
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion; incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Lack of stigmata of chronic liver disease such as spider angiomata, splenomegaly, or gynecomastia is typical in ALF. Neurologic evaluation should note pupil size and reactivity and reflexes, presence or absence of clonus, and the presence or absence of hepatic encephalopathy. Grade of encephalopathy is to be assessed (Table 1). The neurologic evaluation needs to be monitored frequently in patients who have rapidly accelerating disease, as changes may occur in hours.

Initial laboratory examination must be extensive in order to evaluate both the etiology and severity of ALF. Early testing should include complete blood count, blood sugar, arterial blood gas measurements, blood typing, acetaminophen level and screens for other drugs and toxins, viral serologies (Table 2), tests for Wilson disease, autoantibodies and a pregnancy test in females. Plasma ammonia, preferably arterial, may also be helpful.

A multidisciplinary team consist of transplant surgeons, hepatologists, and intensivists, radiologists, anesthesiologists and neurologists should be involved in the care of ALF. Daily communication between the caring team and the patient's family is very important given the rapidly changing clinical picture.

Viral hepatitis: Viral hepatitis A and E related ALF must be treated with supportive care as no virus-specific treatment has proven to be effective. Nucleotide analogs should be considered for hepatitis B-associated ALF and for prevention of post-transplant recurrence. Patients with known or suspected herpes virus or varicella zoster as the cause of ALF should be treated with acyclovir (5–10 mg/kg IV every 8 hours and may be considered for transplantation).

Acetaminophen hepatotoxicity: Acetaminophen hepatotoxicity is suggested by historic evidence for excessive ingestion either as suicidal intention or the inadvertent use

by mansdocs.com

Table 2: Initial laboratory analysis.

Prothrombin time/INR

- Chemistries
  - Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate glucose
  - AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin creatinine and blood urea nitrogen
- Arterial blood gas
- Arterial lactate
- Complete blood count
- Blood type and screen
- Acetaminophen level
- Toxicology screen
- Viral hepatitis serologies
  - anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HEV, anti-HCV, HCV RNA*, HSV1 IgM, VZV
- Ceruloplasmin level#
- Pregnancy test (females)
- Ammonia (arterial if possible)
- Autoimmune markers
  - ANA, ASMA, Immunoglobulin levels
- HIV-1, HIV-2
- Amylase and lipase

*Done to recognize potential underlying infection.

#Done only if Wilson disease is a consideration (e.g. in patients < 40 years without another obvious explanation for ALF); in this case uric acid level and bilirubin to alkaline phosphatase ratio may be helpful as well.

Source: Produced from AASLD position paper: The management of Acute Liver Failure: Update 2011.

(INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-Glutamyl transferase; HAV: Hepatitis A virus; HCV: Hepatitis C virus; HSV: Herpes simplex virus; VZV: Varicella-zoster virus; ANA: Antinuclear antibody; ASMA: Antismooth muscle antibody; HIV: Human immunodeficiency virus).

of supratherapeutic quantities of pain medications. Very high aminotransferase levels are typically seen; serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning. If acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation, activated charcoal may be useful for gastrointestinal decontamination. While it is most effective if given within 1 hour of ingestion, it may be of benefit as long as 3–4 hours after ingestion. N-acetylcysteine (NAC), the antidote for acetaminophen poisoning, should be given as early as possible, but may still be of value 48 hours or more after ingestion. Acetaminophen is metabolized in hepatocytes by cytochrome enzymes to the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI is normally detoxified by conjugation with glutathione. Depletion of glutathione leads to accelerated liver injury by virtue of reduced detoxification of NAPQI. NAC is administered to patients with toxic acetaminophen ingestion to replenish glutathione stores. In addition NAC also provide substrate for hepatic ATP synthesis thus supports the mitochondrial energy metabolism. Acetaminophen induced injury is concentrated in the central zones of the liver, and portal tracts are mostly spared excepting in extreme injury, permitting spontaneous recovery in as many as 80% with timely NAC therapy. NAC may be given orally (140 mg/kg by mouth or nasogastric tube diluted to 5% solution, followed by 70 mg/kg by mouth q 4 h × 17 doses). Oral administration has largely been replaced by intravenous administration (loading dose is 150 mg/kg in 5% dextrose over 15 minutes; maintenance dose is 50 mg/kg given over 4 hours followed by 100 mg/kg administered over 16 hours or 6 mg/kg/h). Controversy exists over when to stop use of NAC, whether a standard 72-hour period is optimal or continuation until liver chemistry values have improved.

Nonacetaminophen ALF for patients whose disease appears to be caused by etiologies other than acetaminophen, N-acetylcysteine may improve outcomes. In a randomized, controlled trial, NAC appeared to improve spontaneous survival when given during early coma stages (grades I and II) in the setting of nonacetaminophen ALF including, for example, drug-induced liver injury and hepatitis B.

Other Causes of ALF

Patient with mushroom poisoning presented with the history of severe gastrointestinal symptoms like nausea, vomiting, diarrhea and abdominal cramping. It can occur in hours to days after ingestion of mushroom. Amantinin toxin, recycled via enterohepatic circulation, interrupts hepatocyte mRNA synthesis. Thus, it results dose-dependent hepatotoxicity. Initial treatment includes gastric lavage and activated charcoal. NAC infusion is helpful. Mortality in ALF secondary to mushroom poisoning approaches 10–30%. Penicillin G and silibinin may ameliorate the hepatic injury; however, patients should be listed for liver transplantation, because this procedure is often the only life-saving option.

Metabolic ALF may result from underlying metabolic liver disease. Liver failure caused by copper toxicosis in Wilson disease is unusual unless there is underlying liver

by mansdocs.com

disease is present. ALF caused by Wilson disease typically is accompanied by a nonimmune hemolytic anemia, and may be recognized by a low alkaline phosphatase to bilirubin ratio (less than four) and alanine transaminase (ALT) to aspartate transaminase (AST) ratio of less than 2, markedly elevated serum copper greater than 200 mg/dL, and 24-hour urine copper often greater than 200 mg. A low alkaline phosphatase to bilirubin can be obtained much more rapidly than urinary or serum copper in Wilson's disease. Renal function is often impaired as the released copper can cause renal tubular damage. Treatment to acutely lower serum copper and to limit further hemolysis should include albumin dialysis, continuous hemofiltration, plasmapheresis, or plasma exchange. Initiation of treatment with penicillamine is not recommended in ALF as there is a risk of hypersensitivity to this agent.

Acute fatty liver of pregnancy is an unusual disorder where the metabolic disruption in the fetus causes maternal-fetal distress. This disorder typically presents in the third trimester with marked elevation of liver tests and may progress rapidly to jaundice and liver failure. ALF occurs when mitochondrial dysfunction due to maternal and fetal fatty acid β-oxidation defects resulting in microvascular fatty acid accumulation in hepatocytes. There is an overlap of these two clinical syndromes, and they play a major role in the pathogenesis of preeclampsia, with hypertension, and proteinuria. Early recognition of these syndromes and prompt delivery are critical in achieving good outcomes. Failure to recover from the illness should be promptly listed for liver transplantation. The hepatic damage of HELLP syndrome is proposed to result from disordered placentation, leading to either the circulation of antiangiogenic factors and endothelial dysfunction, or cytokine production causing the characteristic periportal hemorrhage.

ICU Management of ALF

The mortality in ALF is as high as 40–50% depending upon the cause and improper therapeutic management. The immediate cause of death in ALF patient is mainly because of brain herniation due to raised intracranial hypertension and multiorgan failure following sepsis.

Outline of ICU Management

Cerebral Edema/Intracranial Hypertension:

Grade I/II Encephalopathy

- Consider transfer to liver transplant facility and listing for transplantation
- *Brain CT*: Rule out other causes of decreased mental status; little utility to identify cerebral edema
- Avoid stmulation; avoid sedation if possible
- *Antibiotics*: Surveillance and treatment of infection required; prophylaxis possibly helpful
- Lactulose, possibly helpful.

Grade III/IV Encephalopathy

- Continue management strategies listed above
- Intubate trachea (may require sedation)
- Elevate head of bed
- Consider placement of ICP monitoring device
- Immediate treatment of seizures required; prophylaxis of unclear valve
- *Mannitol*: Use for severe elevation of ICP or first clinical signs of herniation
- Hypertonic saline to raise serum sodium to 145–155 mmol/L
- *Hyperventilation*: Effects short-lived; may use for impending herniation.

Infection

- Surveillance for and prompt antimicrobial treatment of infection required
- Antibiotic prophylaxis possibly helpful but not proven.

Coagulopathy

- *Vitamin K*: Give at least one dose
- *FFP*: Give only for invasive procedures or active bleeding
- *Platelets*: Give only for invasive procedures or active bleeding
- *Recombinant activated factor VII*: Possibly effective for invasive procedures
- *Prophylaxis for stress ulceration*: Give H_2 blocker or PPI.

Hemodynamics/Renal Failure

- Volume replacement
- Pressor support (dopamine, epinephrine, norepinephrine) as needed to maintain adequate mean arterial pressure (MAP)
- Avoid nephrotoxic agents
- Continuous modes of hemodialysis if needed
- Vasopression recommended in hypotension refractory to volume resuscitation and norepinephrine.

Metabolic Concerns

- *Follow closely*: Glucose, potassium, magnesium, phosphate
- *Consider nutrition*: Enteral feeding if possible or total parenteral nutrition.

by mansdocs.com

Management of Intracranial Hypertension

As soon as patient is received in ICU, patient's neurological status should be examined and recorded. Encephalopathy grades 3 and 4, elevated serum ammonia (greater than 150–200 mm), rapid progression to hepatic encephalopathy, infection or systemic inflammatory syndrome (SIRS), and requirement for vasopressor support or renal replacement therapy are recognized clinical risk factor of cerebral edema. Invasive intracranial pressure (ICP) monitoring remains the only objective standard for measuring and monitoring intracranial hemorrhage (ICH). However in clinical practice, ICP monitoring for patients who have ALF remains controversial. Neuroimaging is not reliable in diagnosing early ICH but may help to exclude other problems such as intracranial bleeding or stroke.

Intracranial Hypertension: General Management Principles

Patients should be kept in a quiet room with minimal stimulus. Head end of the bed should be elevated to 30–45°. It helps in draining CSF. Any flexion and rotation of neck should be avoided. Threshold for intubation of trachea should be kept low. Grade 3 or more HE patient's trachea should be intubated electively. Patients should be put on mechanical ventilation with controlled ventilation. Sedation is established with propofol and fentanyl infusion. Dose of sedative is titrated with requirement of patient and maintenance of hemodynamics. Fentanyl is a first line of analgesics in ALF. Morphine is not preferred because of active metabolite. Propofol is a very good drug for sedation in this setting. Normocapnea is maintained. Patient with ALF may have associated acute lung injury. One needs to maintain oxygenation and prevent hypercapnea. But it is often difficult to maintain normocapnea in the setting of low tidal volume in case of ALI. Even high positive end expiratory pressure (PEEP) can cause theoretical rise of ICP. In general lowest PEEP that maintains the oxygenation should be used. There should be infrequent endotracheal suctioning with maintaining adequate sedation. Fevers should be controlled by cooling, because acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, and rigoring or shivering also avoided, as these may exacerbate ICP. When invasive monitoring is available, the ICP should be maintained below 25 mm Hg. The MAP should be adequate to maintain cerebral perfusion pressure (CPP) between 50 mm Hg and 80 mm Hg. Prolonged ICP more than 40 mm Hg and CPP less than 50 mm Hg are associated with a poor outcome.

Role of ICP Monitoring

Clinical features of raised ICP like systemic hypertension, bradycardia and irregular respirations–Cushing's triad are not uniformly present, and other neurologic changes such as pupillary dilatation or signs of decerebration are typically evident only late in the course. Furthermore, CT of the brain does not reliably demonstrate evidence of edema especially at early stages. Moreover refractory ICH and/or decreased CPP are considered relative contraindications to liver transplantation in many centers because of concern about poor neurological recovery. Monitoring the ICP, although contentious because of its invasive nature, allows early detection of raised ICP and assessment of the CPP, calculated as mean arterial pressure-intracranial pressure (MAP-ICP). This can help in early initiation of therapy and avoidance of hypoxic injury that may result from hypoperfusion of the brain and may improve the neurological outcomes in ALF patient. ICP monitoring may be most important tool in operation theater during liver transplantation, where the risk of developing worsening cerebral edema is highest during reperfusion. This may be compounded by hemodynamic instability in a critically ill ALF patient. Invasive monitoring device like placement of a catheter in epidural space was used to monitor ICP. The unreliability of pressure monitoring in the epidural space was improved by placement in subdural or intraparenchymal locations, but complications also increased. Intracranial bleeding, an oftencited complication of ICP monitoring, is encountered in 10–20% of patients. Most intracranial bleeding is mild and of little clinical significance. Among patients who have severe coagulopathy, reduction of INR has been managed successfully with the use of recombinant factor VIIa. Correction of coagulopathy should be continued for approximately 48 hours after the insertion of probes/catheters to prevent bleeding. Undoubtedly, the experience of the team in placing ICP monitors is important in keeping this complication rate low. Despite lack of consensus, many centers place ICP monitors to actively manage cerebral edema in patients who have advanced (stage 3 or 4) encephalopathy.

Other methods of monitoring ICP (such as transcranial doppler ultrasonography, near-infrared spectrophotometry are in various stages of evaluation, but have thus far not been proven reliable in estimating ICP.

by mansdocs.com

Measurement of optic nerve sheath diameter and jugulovenous oxygen saturation ($SVjO_2$) can be used as an indirect marker for assessing raised intracranial pressure. The normal range of $SVjO_2$ is 65–80%. High values of $SVjO_2$ may be indicative of cerebral hyperemia and low values may be indicative of relative ischemia. So it provides both a guide for the targeting of ICP monitoring as well as for therapies likely to affect cerebral perfusion and metabolic activity.

Meticulous attention needs to be paid to metabolic and acid-base abnormalities including hyper- and hypoglycemia, hyponatremia, hyperlactatemia, and hypercapnia, as these have been shown to contribute to higher ICP. Blood sugar to be checked every 2nd hourly. Blood sugar is maintained between 100 mg/dL and 180 mg/dL. 20% mannitol is often used as first-line therapy to decrease ICP. Serum osmolality should be checked regularly and it should be kept below 320 mOsm/L. Its use is limited once patients develop significant renal injury. In contrast to Mannitol, hypertonic saline can be used as a prophylactic measure with few adverse effects, with a goal of achieving serum sodium of 145–155 mEq/L. Evidence, however, is limited to a single randomized controlled trial, and hypertonic saline never has been tested formally as a treatment of established ICH in patients who have ALF.

Phenytoin may reduce cerebral edema regardless of seizure activity. Rifaximin may be used to lower ammonia. A detailed analysis of serum ammonia in patients with ALF identified a concentration of 75 μg/dL as an important threshold below which patients rarely develop ICH. Conversely, arterial ammonia levels of more than 100 μg/dL on admission represent an independent risk factor for the development of high-grade hepatic encephalopathy, and a level of more than 200 μg/dL predicts ICH. There is no role for corticosteroids given cerebral edema is of cytotoxic origin, as opposed to vasogenic origin in the patient who has ALF.

Moderate hypothermia (32°C to 33°C) appears to be a good tool for managing ICP. However, considering the side effect of hypothermia, unlike in traumatic brain injury it is infrequently used tool in ALF.

Management of Hemodynamics

Like chronic liver disease hemodynamic status is characterized by high cardiac output and low systemic vascular resistance. So it closely mimics septic shock, and differentiating between the two can be challenging. Hypotension is quite common. Besides this, the patient may be hypovolemic because of poor intake and concurrent administration of drugs like mannitol. Volume status should be assessed before starting IV fluids or vasopressors. This may necessitate central pressure monitoring or indirect estimates of volume by measurement of end diastolic volume in the heart by echocardiography or measuring inferior vena cava (IVC) diameter. A cardiac index of less than 3.5 L/min/m^2 with evidence of inadequate tissue perfusion despite apparent euvoluemia should be treated with inotropic agents. Vasopressors can be used adjunctively to maintain a MAP above 65 mm Hg, with a goal CPP of 50–80. Surges in MAPs also should be avoided as this may lead to cerebral hyperemia. Norepinephrine should be preferred, as it is associated with consistent and predictable increases in CPP. Relative adrenal insufficiency occurs frequently, but treatment with moderate-dose of corticosteroids is reserved for those unresponsive to pressors.

Management of Coagulopathy

Acute liver failure is a state where there is an imbalance between the procoagulant and anticoagulant. Deficiencies of fibrinolytic proteins, anticoagulant proteins (protein C/S or antithrombin III) and procoagulation factors (II, V, VII, IX and X) are often present in ALF; in part due to failure of synthesis as well as consumption of these factors. So despite severe derangements in coagulation profile, clinically significant spontaneous bleeding remains relatively uncommon. Prophylactic transfusions to normalize coagulation profile in all patients who have ALF are unnecessary as it has not been shown to alter the risk of significant bleeding or future transfusion requirement. Rather it can cause volume overload which may be detrimental in presence of ALI or AKI. It also obscures the trend of prothrombin time. Because subclinical vitamin K deficiency contributes to coagulopathy in up to 25% of patients, empiric administration of vitamin K 10 mg intravenously given as a single dose is recommended. In general, infusion of fresh frozen plasma is indicated only for control of active bleeding or during invasive procedures such as insertion of ICP monitor, to maintain an INR less than 1.5. When fresh frozen plasma fails to normalize PT/INR adequately, the use of recombinant factor VIIa can be considered. Platelet transfusion is indicated only to aid in controlling active bleeding or during invasive procedures if the count is less than 50×10^9/L or prophylactically if less than 15×10^9/L. Concomitant administration of cryoprecipitate is recommended for patients who have significant hypofibrinogenemia (< 1 g/L).

by mansdocs.com

Renal Failure Management

Incidence of renal failure in ALF is as high as 50–80%. Acute renal failure resembling hepatorenal syndrome is multifactorial in the setting of ALF. Often the patient is hypovolemic due to poor oral intake due to encephalopathy and concomitant use of drugs like mannitol and nephrotoxic drugs. Renal injury is accentuated in presence of hypovolemia. Ischemia from hypotension can cause acute tubular necrosis. Before starting any renal replacement therapy it is important to find out whether the patient is euvolemic or not. In addition, development of abdominal compartment syndrome, due to ascites, intra-abdominal hemorrhage or severe abdominal and gut wall edema, is a common cause of renal impairment in ALF. Management includes avoidance of nephrotoxic agents, treatment of infection, and maintenance of adequate renal perfusion. In patients who have worsening renal function or acidemia, renal replacement therapy should be started early to avoid volume overload and to help with control of acid-base status and electrolyte balance. Continuous renal replacement therapy is recommended, because most patients with ALF tolerate intermittent hemodialysis poorly because of circulatory instability, precipitous fluid shifts and a rise in ICP.

Infectious Disease Considerations

Infections are the most common cause of death and morbidity in patients who have ALF. Like chronic liver disease in ALF, Kuppfer cell function is impaired, and clearance of normal gut bacteria that translocate is less efficient. Several defects of innate immunity in ALF affecting the complement system, neutrophil cell function have been demonstrated. ALF patients have qualitative and quantitative changes in both classical and alternative complement pathways; well documented are the defects of C3, C5 and CH50. In vitro studies have shown that serum from ALF patients is deficient in C3 and C5 has reduced opsonic capacity against *Escherichia coli* and yeasts, and poor chemoattractant ability for neutrophils. This increases the risk of infection. The most common site of bacterial infection is the lung, then urinary tract and blood. The most frequently identified organisms are *Staphylococcus*, *Streptococcus* and enteric Gram-negative bacilli. *Candida albicans* is the most common fungal infection. Catheter-related sepsis is a serious concern, and avoidance of unnecessary intravenous lines and careful attention to proper hygiene and changing of access are important. Infection develops early in the course of ALF, with a median onset time of 2–5 days following admission to hospital and is responsible for late death in at least a quarter of cases.

On admission, a chest radiograph is performed, and urinalysis and urine, and paired blood cultures should be obtained routinely. For any patient on a ventilator, sputum smear and cultures also should be obtained. Empiric use of antibiotics is recommended. The choice of an antimicrobial agent must take into account the need to cover a broad spectrum of Gram-positive and Gram-negative organisms as per the local sensitivity pattern.

King's College group documented the association of infection with progression of encephalopathy through activation of SIRS leading to poor prognosis. A recent report by Schmidt and Larsen confirmed that the presence of SIRS in ALF carries a poor prognosis and also identified correlations between sequential organ failure assessment score (SOFA), disease severity and SIRS components. The relatively recent introduction of corticosteroids in the treatment of functional adrenal insufficiency associated with circulatory shock in ALF may further increase susceptibility to infections. Despite improvement in medical care and routine use of prophylactic antibiotics, sepsis remains a major cause of mortality in ALF.

Nutrition

Patients are prone to hypoglycemia in acute liver injury because of loss of glycogen stores, impairment of gluconeogenesis, and increased circulating insulin. Rapid development of hypoglycemia, which can confound the hepatic encephalopathy, should be managed with continuous intravenous glucose infusion. Hyperglycemia should also be avoided because it may contribute to poor ICP control. Since ALF patients are catabolic early nutritional supplementation is very crucial. In minimal HE, patient can be fed orally. If oral feeding is discontinued, then enteral supplementation should be initiated. Caloric goals for patients who have ALF should be approximately 25–30 kcal/kg/d. Protein intake should be kept around 1–1.5 g/kg/d. Excess glutamine supplementation should be avoided in ALF, as it may lead to development of cerebral edema, due to its role in production of ammonia. Vitamin B-complex, C and trace elements should be supplemented in the critically ill patient.

by mansdocs.com

Table 3: King's criteria for increased mortality in acute liver failure.

Acetaminophen-induced ALF	*Nonacetaminophen-induced ALF*
• Strongly recommended list for OLT if:	• List for transplantation if:
– Arterial lactate > 3.5 mmol/L after early fluid resuscitation	– INR > 6.5 and encephalopathy present irrespective of grade
• List for transplantation if:	• Or if any three of the following features (encephalopathy irrespective of grade) are present:
– Arterial pH < 7.3 or arterial lactate > 3.0 mmol/L after adequate fluid resuscitation	– Age < 10 year or > 40 year – Interval from jaundice to encephalopathy < 7 d
• List for transplantation if all three of the following occur within a 24-hour period:	– INR ≥ 3.5
– Grade 3 or 4 hepatic encephalopathy	– Serum bilirubin ≥ 300 µmol/L
– INR > 6.5	– Unfavorable etiology, such as seronegative hepatitis, idiosyncratic drug reaction or Wilson disease
– Creatinine > 300 µmol/L	

(ALF: Acute liver failure; OLT: Orthotopic liver transplantation; INR: International normalized ratio).

Prediction for Spontaneous Recovery

Decision as to whether a patient will recover with conservative management or require transplantation is a debate. However, the King's College Hospital (KCH) Criteria remains the current standard for clinicians. These criteria are used to predict death in patients presenting with ALF in the setting of acetaminophen and other causes of ALF (Table 3). Patients who had a high probability of death were considered to be candidates for liver transplantation. Other studies have attempted to look at etiology-specific indices (Dhawan and colleagues and Korman and colleagues for Wilson disease) or have tried to use other additional serum-based tests to help predict survival. Serum phosphate levels in acetaminophen toxicity may be used adjunctively along with the King's criteria to help with the clinical decision as to whether to move toward transplant. KCH criteria has a sensitivity of 68–69% and specificity of 82–92%. The Clichy criteria were developed in acute HBV infection. A serum factor V level of less than 20% in patients younger than 30 years or less than 30% in any patient with grade 3–4 HE predicted mortality with a positive predictive value of 82% and a negative predictive value of 98%. Factor V level measurements are less readily available than the measures in the KCH criteria, and subsequent studies have shown these criteria to be less accurate than the KCH criteria in predicting outcome. Decision making with respect to the timing of transplantation is difficult for transplant surgeons and hepatologists. Although established criteria such as King's College criteria have been used to predict poor outcomes without transplantation, the right decision can be made only by the transplant team after following the patient's clinical course and disease progression. Once transplantation is considered, the patient must undergo a rapid multidisciplinary evaluation.

Liver Support Devices

Artificial support therapies provide detoxification support without the use of cellular material. These artificial supports are sorbent-based systems, which detoxify only, employ charcoal or other adherent particles, such as albumin, in a capsule or column device placed in an extracorporeal circuit. The molecular absorbents recirculation system (MARS) is a two-circuit system, which allows albumin-bound toxins to be removed. MARS failed to show a significant survival benefit in ALF patients. The Prometheus albumin dialysis system functions similarly to MARS, however there exists even less data on its survival benefit. Thus, there has been no good evidence that any artificial support system reliably reduces mortality in the setting of ALF. Bioartificial systems utilize cellular material. Theoretically bioartificial device should not only provide detoxification, but also assume many of the liver's synthetic functions. Hepatocytes, whether of human or other mammalian origin, have been used in cartridges in extracorporeal circuits, either with or without sorbent columns. A recent meta-analysis, considering all forms of bioartificial devices together, demonstrated no efficacy for the treatment of ALF. A variety of other strategies have been employed, including exchange transfusion, charcoal hemoperfusion, extracorporeal liver perfusions, and intraportal hepatocyte infusions. To date, none can be recommended, and their use remains experimental.

LIVER TRANSPLANTATION

Liver transplantation is emerged as the only therapeutic option with proven benefit in advanced ALF. Rapid evaluation for transfer to a transplantation center and consideration for liver transplantation is mandatory so that

by mansdocs.com

transplantation can be applied before contraindications develop. Contraindications to transplantation such as substance abuse, suicidal predilection, psychiatric disorders, uncontrollable sepsis and other organ system involvement (irreversible brain damage, extrahepatic malignancy, cardiovascular failure requiring > 1 μg/kg/min norepinephrine infusion, and ARDS requiring FiO_2 > 60% and PEEP > 12 cm H_2O) must be excluded. When a suitable liver offer becomes available, transplantation is performed. The availability of deceased donor liver allograft is unpredictable. The impact on survival after liver transplantation in ALF has not been determined. Other established predictors of post-transplantation outcome of ALF patients are still missing.

Future Direction

Although there is randomized controlled trial artificial and bioartificial liver support devices, it may play a role in regeneration of hepatocytes in ALF patient. Hepatocyte transplantation has been proposed for treatment of ALF. In this technique, human hepatocytes are infused into the splenic or hepatic portal vascular beds or peritoneal cavity to provide adjunctive hepatic function for the failing liver.

CONCLUSION

The management of ALF challenges our best skills because of its rapid progression and frequently poor outcomes. Early identification of ALF and the administration of etiology specific treatment are crucial to improve the outcome. A better understanding of the pathophysiology of ALF will probably lead to further improvement in survival rates.

BIBLIOGRAPHY

1. Acharya SK, Panda SK, Saxena A, et al. Acute hepatic failure in India: a perspective from the East. J Gastroenterol Hepatol. 2000;15:473-9.
2. Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. J Hepatol. 1997;26:62-8
3. Bacq Y. Liver diseases unique to pregnancy: a 2010 update. Clin Res Hepatol Gastroenterol. 2011;35:182-93.
4. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. Crit Care Med. 2003;31:299-305.
5. Berman DH, Leventhal RI, Gavaler JS, et al. Clinical differentiation of fulminant Wilsonian hepatitis from other causes of hepatic failure. Gastroenterology. 1991;100:1129-34
6. Bernal W, Hall C, Karvellas CJ, et al. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology. 2007;46:1844-52.
7. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis. 1986;6:97-106.
8. Bhatia V, Singhal A, Panda SK, et al. A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? Hepatology. 2008;48:1577-85.
9. Bianco E, Stroffolini T, Spada E, et al. Case fatality rate of acute viral hepatitis in Italy: 1995–2000. An update. Dig Liver Dis. 2003;35:404-8.
10. Bismuth H, Samuel D, Gugenheim J, et al. Emergency liver transplantation for fulminant hepatitis. Ann Intern Med. 1987;107:337-41.
11. Burnell JM, Dawborn JK, Epstein RB, et al. Acute hepatic coma treated by cross-circulation or exchange transfusion. N Engl J Med. 1967;276:935-43.
12. Canalese J, Wyke RJ, Vergani D, et al. Circulating immune complexes in patients with fulminant hepatic failure. Gut. 1981;22:845-8.
13. Castro MA, Fassett MJ, Reynolds TB, et al. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol. 1999;181:389-95.
14. Chari RS, Collins BH, Magee JC, et al. Brief report: treatment of hepatic failure with ex vivo pig-liver perfusion followed by liver transplantation. N Engl J Med. 1994;331:234-7.
15. Clapperton M, Rolando N, Sandoval L, et al. Neutrophil superoxide and hydrogen peroxide production in patients with acute liver failure. Eur J Clin Invest. 1997;27:164-8.
16. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology. 1977;72:573-83.
17. Dalton HR, Bendall R, Ijaz S, et al. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis. 2008;8:698-709.
18. Davies MH, Mutimer D, Lowes J, et al. Recovery despite impaired cerebral perfusion in fulminant hepatic failure. Lancet. 1994;343:1329-30.
19. Detry O, Arkadopoulos N, Ting P, et al. Intracranial pressure during liver transplantation for fulminant hepatic failure. Transplantation. 1999;67(5):767-70.
20. Devauchelle P, Page M, Brun P, et al. Continuous haemodialysis with citrate anticoagulation in patients with liver failure: three cases. Ann Fr Anesth Reanim. 2012;31:543-6.
21. Dhawan A, Taylor RM, Cheeseman P, et al. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl. 2005;11:441-8.

by mansdocs.com

22. Gow PJ, Sood S, Angus PW. Serum phosphate as a predictor of outcome in acetaminophen-induced fulminant hepatic failure. Hepatology. 2003;37:711-2.
23. Green R, Grierson R, Sitar DS, et al. How long after drug ingestion is activated charcoal still effective? J Toxicol Clin Toxicol. 2001;39:601-5.
24. Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet. 1990;335: 1572-3.
25. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology. 2002;36:395-402.
26. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. Liver Int. 2003;23:71-7.
27. Heard K, Green JL, Bailey JE, et al. A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Aliment Pharmacol Ther. 2007;26:283-90.
28. Jalan R, Olde Damink SW, Deutz NE, et al. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology. 2004; 127:1338-46.
29. Jalan R, Williams R, Bernuau J. Paracetamol: are therapeutic doses entirely safe? Lancet. 2006;368:2195-6.
30. Jhang JS, Schilsky ML, Lefkowitch JH, et al. Therapeutic plasmapheresis as a bridge to liver transplantation in fulminant Wilson disease. J Clin Apher. 2007;22:10-4.
31. Khan SA, Shah N, Williams R, et al. Acute liver failure: a review. Clin Liver Dis. 2006;10:239-58.
32. Khuroo MS, Farahat KL. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transpl. 2004;10:1099-106.
33. Khuroo MS, Kamili S. Aetiology and prognostic factors in acute liver failure in India. J Viral Hepat. 2003;10:224-31.
34. Khuroo MS, Kamili S. Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers. J Viral Hepat. 2009;16:519-23.
35. Korman JD, Volenberg I, Balko J, et al. Screening for Wilson disease in acute liver failure: A comparison of currently available diagnostic tests. Hepatology. 2008;48:1167-74.
36. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42:1364-72.
37. Larson AM. Acute liver failure. Dis Mon. 2008;54(7): 457-85.
38. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137:856-64.
39. Lee WM, Larson AM, Stravitz RT. AASLD position paper: The management of acute liver failure: Update 2011. Hepatology. 2012;55(3):965-7.
40. McCashland TM, Shaw BW, Tape E. The American experience with transplantation for acute liver failure. Semin Liver Disease. 1996;16:427-33.
41. McKenzie TJ, Lillegard JB, Nyberg SL. Artificial and bioartificial liver support. Semin Liver Dis. 2008;28:210-7.
42. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of King's College Hospital Criteria in prediction of outcome in nonparacetamol-induced acute liver failure. J Hepatol. 2010;53:492-9.
43. Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. Clin Gastroenterol Hepatol. 2006;4:1076-81.
44. Miners JO, Drew R, Birkett DJ. Mechanism of action of paracetamol protective agents in mice in vivo. Biochem Pharmacol. 1984;33:2995-3000.
45. Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology. 1991;13: 209-12.
46. Munoz SJ, Stravitz RT, Gabriel DA. Coagulopathy of acute liver failure. Clin Liver Dis. 2009;13:95-107.
47. Munoz SJ. The hepatorenal syndrome. Med Clin North Am. 2008;92:813-37.
48. Murphy N, Auzinger G, Bernal W, et al. Effect of hypertonic sodium chloride on intracranial pressure in patient with acute liver failure. Hepatology. 2002;39:464-70.
49. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947-54.
50. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137: 947-54.
51. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97:439-55.
52. O'Grady JG, Gimson AE, O'Brien CJ, et al. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology. 1988;94:1186-92.
53. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342:273-5.
54. Patra S, Kumar A, Trivedi SS, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med. 2007;147:28-33.
55. Ranek L, Andersen V, Jarnum S, et al. Extracorporeal irradiation of the blood: attempted immunosuppressive treatment of active, non-alcoholic cirrhosis. Scand J Gastroenterol. 1971;6:389-96.
56. Rolando N, Gimson A, Wade J, et al. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology. 1993;17:196-201.
57. Rolando N, Harvey F, Brahm J, et al. Fungal infection: a common, unrecognised complication of acute liver failure. J Hepatol. 1991;12:1-9.
58. Rolando N, Harvey F, Brahm J, et al. Prospective study of bacterial infection in acute liver failure. Hepatology. 1990; 11:49-53.

by mansdocs.com

59. Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis. 1996; 16:389-402.
60. Rolando N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000;32:734-9.
61. Rutherford A, Chung RT. Acute liver failure: mechanisms of hepatocytes injury and regeneration. Semin Liver Dis. 2008;28:167–74.
62. Santi L, Maggioli C, Mastroroberto M, et al. Acute liver failure caused by amanita phalloides poisoning. Int J Hepatol. 2012;2012:487480.
63. Sato RL, Wong JJ, Sumida SM, et al. Efficacy of superactivated charcoal administration late (3 hours) after acetaminophen overdose. Am J Emerg Med. 2003;21:189-91.
64. Schilsky ML. Diagnosis and treatment of Wilson's disease. Pediatr Transplantation. 2002;6:15-9.
65. Schiodt FV, Atillasoy E, Shakil AO, et al. Aetiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg. 1999;5:29-34.
66. Schiodt FV, Rochling FJ, Casey DL, et al. Acetaminophen toxicity in an urban county hospital. N Engl J Med. 1997;337: 1112-7.
67. Schmidt LE, Larsen FS. MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. Hepatology. 2007;45:789-96
68. Schmidt LE, Larsen FS. Prognostic implications of hyperlactatemia, multiple organ failure, and systemic inflammatory response syndrome in patients with acetaminophen-induced acute liver failure. Crit Care Med. 2006;34: 337-43.
69. Song G, Li Y, Li M, et al. Acute renal and liver failure due to acute fatty liver of pregnancy-complicated preeclampsia. J Obstet Gynaecol. 2012;32:702-3.
70. Strand S, Hofmann WJ, Grambinler A, et al. Hepatic failure and liver cell damage in acute Wilsons disease involve CD95 (APO-1/Fas)-mediated apoptosis. Nat Med. 1998;4:588-93.
71. Sánchez-Bueno F, García Pérez R, Torres Salmerón G, et al. HELLP syndrome with severe liver dysfunction: a presentation of three cases. Cir Esp. 2012;90:33-7.
72. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and ad- verse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr. 2012;161:88-93.
73. Taylor RM, Davern T, Munoz S, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. Hepatology. 2006;44:1589-97.
74. Temple AR, Lynch JM, Vena J, et al. Aminotransferase activities in healthy subjects receiving three-day dosing of 4, 6, or 8 grams per day of acetaminophen. Clin Toxicol (Phila). 2007;45:36-44.
75. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282-98.
76. Trey C, Lipworth L, Chalmers TC, et al. Fulminant hepatic failure. Presumable contribution to halothane. N Engl J Med. 1968;279:798-801.
77. Trost LC, Lemasters JJ. Role of the mitochondrial permeability transition in salicylate toxicity to cultured rat hepatocytes: implications for the pathogenesis of Reye's syndrome. Toxicol Appl Pharmacol. 1997;147:431-41.
78. Vaquero J, Fontana RJ, Larson AM, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl. 2005;11:1581-9.
79. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology. 2003;125:755-64.
80. Walsh TS, Wigmore SJ, Hopton P, et al. Energy expenditure in acetaminophen-induced fulminant hepatic failure. Crit Care Med. 2000;28:649-54
81. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. World J Gastroenterol. 2013; 19(41):7069-77.
82. Ward J, Kapadia K, Brush E, et al. Amatoxin poisoning: case reports and review of current therapies. J Emerg Med. 2013; 44:116-21.
83. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006;296:87–93.
84. Williams R. Classification, aetiology, and considerations of outcome in acute liver failure. Semin Liver Dis. 1996;16: 343-8.
85. Willner IR, Uhl MD, Howard SC, et al. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med. 1998;128: 111-4.
86. Wyke RJ, Rajkovic IA, Eddleston AL, et al. Defective opsonisation and complement deficiency in serum from patients with fulminant hepatic failure. Gut. 1980;21:643-9.
87. Wyke RJ, Yousif-Kadaru AG, Rajkovic IA, et al. Serum stimulatory activity and polymorphonuclear leucocyte movement in patients with fulminant hepatic failure. Clin Exp Immunol. 1982;50:442-9.
88. Yeo W, Zee B, Zhong S, et al. Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer. 2004;90:1306-11.
89. Zimmerman JH, Maddrey WC. Acetaminophen (paracetamol) hepatoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology. 1995;22:767-73.

by mansdocs.com

CHAPTER

26

Acute Pancreatitis

Yogesh Batra, Ashish Garg

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory process and is one of the common medical disorders that require an emergent care. Recognizing patients with severe AP as soon as possible is critical for achieving optimal outcomes. Clinical history, leads to the working diagnosis, which is supported by the laboratory tests and may define etiology and complications. Imaging is required if diagnosis is in doubt and in severe pancreatitis.

Management depends upon severity. Symptomatic management is what all is required in a mild case. In a severe case, management involves aggressive supportive care, prevention of infections, organ support and treatment of complications. Surgical intervention is indicated in selected cases.

ETIOLOGY

The most common causes of AP are gallstones (40–70%) and alcohol (25–35%). Gallstone pancreatitis is usually an acute event and resolves when the stone is removed or passes spontaneously.

Alcohol-induced pancreatitis manifestations range from discrete episodes of AP to chronic pancreatitis. Diagnosis should not be entertained unless a person is having greater than 5 years of heavy alcohol intake (>50 g). Less than 5% of heavy drinkers have AP, thus signifying the fact that other factors (genetics, etc.) likely sensitize individuals to effects of alcohol.

Less common causes include:

- *Post-endoscopic retrograde cholangiopancreatography (ERCP)*: Probably the third most common cause. About 5% risk of pancreatitis.
- *Trauma*: Penetrating injuries (knives, bullets), more likely than blunt trauma.
- *Drugs*: Definitely associated with pancreatitis—azathioprine, sulfonamides, valproic acid, methyldopa, furosemide, 6-mercaptopurine, pentamidine, cortico steroids.
- *Infection*: Viral (e.g. mumps virus, coxsackie virus, cytomegalovirus (CMV), hepatitis virus, Epstein-Barr virus (EBV), echovirus, varicella-zoster virus (VZV), measles virus and rubella virus), bacterial (e.g. *Mycoplasma pneumoniae, Salmonella, Campylobacter* and *Mycobacterium tuberculosis*), parasitic (*Ascaris*).
- *Hereditary pancreatitis*: PRSS1, gain-of-function mutation (worldwide), SPINK1 (in India), CFTR mutations, etc.
- *Hypercalcemia*: Hyperparathyroidism, excessive doses of vitamin D, familial hypocalciuric hypercalcemia and total parenteral nutrition (TPN).
- *Developmental anomalies of pancreas*: Sphincter of Oddi dysfunction, pancreas divisum, annular pancreas (rare).
- *Hypertriglyceridemia*: Usually if triglyceride levels greater than 1,000 mg/dL—type I and type V hyperlipidemia.
- *Toxins*: Organophosphorus poisoning, scorpion stings, snake bites.
- Vasculitis
- Idiopathic AP.

by mansdocs.com

EPIDEMIOLOGY

Globally the annual incidence of pancreatitis reported is 13-70 cases per 100,000 persons. At the All India Institute of Medical Sciences (AIIMS), New Delhi, 276 patients with AP were hospitalized from January 1997 to June 2002, i.e. about 55 patients per year. This is about the same as in similar centers in England. The incidence of AP has, however, been reported to be much higher in the USA, Finland and Scotland (49.3, 46.6 and 41.9 per 100,000 population, respectively).

Males are more often affected than females. In males the most common cause is alcohol and in females it is often biliary tract disease.

The median age at onset depends on the etiology:

- Alcohol-related—39 years
- Biliary tract-related—69 years
- Trauma-related—66 years
- Drug-induced etiology—42 years
- ERCP-related—58 years
- AIDS-related—31 years
- Vasculitis-related—36 years.

ASSESSMENT OF SEVERITY

Since the morbidity and mortality of AP differ markedly between mild and severe disease (mild < 5% vs severe 20–25%), it is very important to assess severity as early as possible. Multiple clinical criteria, biochemical parameters and imaging criteria have been used for this purpose.

A very simple clinical severity assessment tool has appeared recently; it is called the bedside index for severity in acute pancreatitis (BISAP) after the following five criteria used:

1. Blood urea nitrogen (BUN) greater than 25 mg/dL
2. Impaired mental status (Glasgow coma scale score <15)
3. Systemic inflammatory response syndrome (SIRS) score greater than or equal to 2
4. Age > 60 years
5. Pleural effusion.

It has been developed from the data of about 18,000 patients with AP and has been tested prospectively and found to be as accurate as acute physiology and chronic health evaluation II (APACHE II) in predicting severity and mortality of AP. The great advantage of this scoring system is ease of its application in day-to-day practice.

Another interesting, very simple clinical tool has been used bedside to assess severity of AP. Absence of rebound tenderness and guarding of the abdomen, normal hematocrit and normal creatinine assure the clinician with 98% certainty that the disease is mild. It is known as harmless acute pancreatitis score (HAPS).

Among the single prognostic markers, hemoconcentration stands out to be a simple, readily available and yet reliable indicator of bad outcome. Thus, a hematocrit of 44% or hemoglobin of 14.6 g/dL or more or a BUN of 33 mg/dL or more are associated with increased pancreatic necrosis and complications. It is because of this that early aggressive fluid replacement is recommended.

Many other single prognostic markers have been suggested. They include obesity (BMI >30), plasma glucose greater than 190 mg/dL, SIRS greater than or equal to 2, trypsinogen-activated peptide (TAP), serum procalcitonin (>3.8 ng/mL), C-reactive protein greater than 150 mg/L, coagulation parameters (e.g. D-dimer), interleukin-6 (>122 pg/mL) and intra-abdominal pressure (>15 mm Hg).

Ranson used a series of different criteria for the severity of AP to formulate a scoring system that is still widely used, however with many drawbacks.

Criteria present on admission include the following:

- Patient older than 55 years
- WBC count higher than 16,000/μL
- Blood glucose level higher than 200 mg/dL
- Serum lactate dehydrogenase (LDH) level higher than 350 IU/L
- Aspartate aminotransferase (AST) level higher than 250 IU/L.

Criteria developing during the first 48 hours include the following:

- Hematocrit fall more than 10%
- BUN level increased by more than 8 mg/dL
- Serum calcium level lower than 8 mg/dL
- PaO_2 less than 60 mm Hg
- Base deficit higher than 4 mEq/L
- Estimated fluid sequestration higher than 6,000 mL.

Each of the above criteria counts for 1 point toward the score. A Ranson score of 0–2 has a minimal mortality, 3–5 has a 10–20% mortality rate, greater than 5 after 48 hours has a mortality of greater than 50% and is associated with more systemic complications.

Ranson criteria has many drawbacks:

- Eleven criteria are used, some of which are evaluated on day 1 and others on day 2. The Ranson score is valid only at 48 hours after onset and not at any other time during the disease.

by mansdocs.com

- The threshold for an abnormal value depends on whether the pancreatitis is caused by alcohol or gallstones.
- Sensitivity and specificity is low.

Acute physiology and chronic health evaluation II is the most widely used method at tertiary care centers. However, it is complicated and requires a long list of parameters to be taken into account. As a result, it is not practical to use it in smaller hospitals with limited staff and expertise.

Contrast-enhanced computed tomography (CECT)-based Balthazar criteria have been used to assess the severity and local complications (Table 1). The severity of the acute inflammatory process is categorized into stage A through E, corresponding to scores of 0–4, respectively. Stage A is when inflammation in minimal (essentially normal pancreas). Stage B represents focal or diffuse gland enlargement, mild heterogeneity of the gland parenchyma and small intrapancreatic fluid collections. Stage C includes, in addition, mild inflammatory changes of the peripancreatic soft tissues. Stage D manifests more prominent peripancreatic inflammatory changes but not more than one ill-defined fluid collection. Stage E represents the most severe stage of inflammation and is manifested by marked intrapancreatic and peripancreatic fluid collections and extraglandular fat necrosis, or frank pancreatic abscess formation.

Necrosis is scored 0 through 6 depending on the extent of pancreas involved (Table 1).

Table 1: Computed tomography severity index (CTSI).

CT grade	*Score*	
A	0	
B	1	
C	2	
D	3	
E	4	
Add to CT score to necrosis score		
Necrosis	*Score*	
None	0	
One-third	2	
One-half	4	
> One-half	6	
CTSI = CT grade score + necrosis score (0–10)		
Index	*Morbidity (%)*	*Mortality (%)*
0–3	8	3
4–6	35	6
7–10	92	17

The sum of scores of grade and necrosis gives computed tomography severity index (CTSI). In Balthazar's series, patients with a CTSI of 0–1 had no mortality or morbidity, while those with an index of 2 had 4% morbidity, and those with an index of 7–10 had 17% mortality and 92% morbidity.

It should be noted, however, that CTSI in isolation fails to predict the outcome and needs to be combined with one or the other clinical criteria to get a reliable assessment of the severity and expected outcome. A modified CTSI has been proposed.

DEFINING THE SEVERITY

The Atlanta classification has been revised recently in 2012–13 and Table 2 shows the salient differences between the new and the previous classification.

Terms used in the new classification based on CECT.

Interstitial edematous pancreatitis: "Inflammation" or stranding in the pancreatic and/or peripancreatic tissues without tissue necrosis.

CECT criteria:

- Pancreatic parenchyma enhances with the contrast agent
- Lack of peripancreatic necrosis.

Table 2: Definitions of severity in acute pancreatitis: comparison of Atlanta and recent revision.

Atlanta criteria (1993)	*Atlanta revision (2013)*
Mild acute pancreatitis	*Mild acute pancreatitis*
Absence of organ failure	Absence of organ failure
Absence of local complications	Absence of local complications
Severe acute pancreatitis	*Moderately severe acute pancreatitis*
1. Local complication AND/OR	1. Local complication AND/OR
2. Organ failure	2. Transient organ failure (<48 hours)
GI bleeding (>500 cc/24 hours)	*Severe acute pancreatitis*
Shock—SBP >90 mm Hg	Persistent organ failure >48 hours*
PaO_2 >60%	
Creatinine >2 mg/dL	

*Persistent organ failure is now defined by a modified Marshall II score (Table 3).

(GI: Gastrointestinal; SBP: Systolic blood pressure).

by mansdocs.com

Table 3: Modified Marshall II score.

	Score				
Organ system	*0*	*1*	*2*	*3*	*4*
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
[serum creatinine (μmol/L)]	≤134	134–169	170–310	311–439	>439
[serum creatinine (mg/dL)]	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (SBP, mm Hg#)	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2
For nonventilated patients, the FiO_2 can be estimated form below:					
Supplemental oxygen (L/min)	FiO_2 (%)				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

*A score of patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/L or ≥1.4 mg/dL.

#Off inotropic support.

Note: A score of 2 or more in any system defines the presence of organ failure.

Necrotizing pancreatitis: Pancreatic parenchymal necrosis and/or peripancreatic necrosis.

CECT criteria:

- Pancreatic parenchymal areas without enhancement by intravenous contrast agent and/or peripancreatic necrosis.

Acute peripancreatic fluid collection: Peripancreatic fluid occurring in the setting of interstitial edematous pancreatitis; this peripancreatic fluid occurs within the first 4 weeks of interstitial edematous pancreatitis.

CECT criteria:

- Homogeneous fluid adjacent to pancreas confined by peripancreatic fascial planes
- No recognizable wall.

Pancreatic pseudocyst: An encapsulated, well-defined collection of fluid but no or minimal solid components which occurs greater than 4 weeks after onset of interstitial edematous pancreatitis.

CECT criteria:

- Well-circumscribed, homogeneous, round or oval fluid collection
- No solid component
- Well-defined wall.

Acute necrotic collection: A collection of both fluid and solid components (necrosis) occur during necrotizing pancreatitis. This collection can involve the pancreatic and/or the peripancreatic tissues.

CECT criteria:

- Heterogeneous, varying of nonliquid density
- No encapsulating wall.
  - Intrapancreatic and/or extrapancreatic.

Walled-off necrosis: A mature, encapsulated acute necrotic collection with a well-defined inflammatory wall; these tend to mature greater than 4 weeks after onset of necrotizing pancreatitis.

CECT criteria:

- Heterogenous liquid and non-liquid density
- Well-defined wall
- Intrapancreatic and/or extrapancreatic.

HISTORY

The cardinal symptom of AP is abdominal pain, which is sudden in onset and gradually intensifies in severity until reaching a constant ache. Most often, it is located in the upper abdomen, usually in the epigastric region. The pain radiates directly through the abdomen to the back in approximately one-half of cases. Nausea and vomiting are often present. Pain frequently improves with the patient in the sitting and forward bending position.

Patients may have a past history of biliary colic and significant alcohol consumption, with or without a recent episode of binge drinking.

by mansdocs.com

PHYSICAL EXAMINATION

The following physical examination findings may be noted, varying with the severity of the disease:

- Fever (76%) and tachycardia (65%) are common
- Abdominal tenderness, muscular guarding (68%) and distention (65%) are observed in most patients; bowel sounds are often diminished or absent because of gastric and transverse colonic ileus
- A minority of patients exhibit jaundice (28%)
- Some patients experience dyspnea (10%), which may be caused by irritation of the diaphragm (resulting from inflammation), pleural effusion, or a more serious condition, such as acute respiratory distress syndrome (ARDS); tachypnea may occur; lung auscultation may reveal basilar rales, especially in the left lung
- In severe cases, hemodynamic instability is evident (10%). Patients with severe AP are often pale and diaphoretic
- Occasionally, in the extremities, muscular spasm may be noted secondary to hypocalcemia.

A few uncommon physical findings are associated with severe necrotizing pancreatitis:

- The Cullen sign is a bluish discoloration around the umbilicus resulting from hemoperitoneum
- The Grey-Turner sign is a reddish-brown discoloration along the flanks resulting from retroperitoneal blood dissecting along tissue planes
- Erythematous skin nodules may result from focal subcutaneous fat necrosis; these are usually not more than 1 cm in size and are typically located on extensor skin surfaces.

Rarely, abnormalities on funduscopic examination may be seen in severe pancreatitis. Termed Purtscher retinopathy, this ischemic injury to the retina appears to be caused by activation of complement and agglutination of blood cells within retinal vessels. It may cause temporary or permanent blindness.

DIAGNOSIS

The definition of AP is based on the fulfillment of at least two of the following criteria:

- Clinical (upper abdominal pain)
- Laboratory (serum amylase or lipase >3 times the upper limit of normal) and/or
- Imaging [computed tomography (CT), magnetic resonance imaging (MRI) ultrasonography] criteria.

Some Important Comments

On admission, the etiology of AP should be determined using detailed personal and family history of pancreatic disease, physical examination, laboratory serum tests and imaging (i.e. right upper quadrant ultrasonography).

Imaging studies (CT) may be useful but are usually not required to diagnose AP. Scenarios where it may be required—sedated patients, clinical suspicion of duodenal perforation, or a prolonged period between onset of symptoms and presentation (lipase and amylase may have normalized).

Routine early CT (<48–72 hours) in AP is not recommended as there is:

- No evidence that it improves clinical outcome or that early detection of necrosis will influence treatment
- CT scoring systems are not superior to clinical scoring systems in predicting prognosis and severity of disease
- Early (inappropriate) CT may increase the duration of hospital stay, has low yield without direct management implications, does not improve clinical outcomes, and poses risks of contrast allergy and nephrotoxicity.

Follow-up CT or MRI in AP is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered.

Although the urinary trypsinogen-2 dipstick test is a rapid and noninvasive bedside test with adequate accuracy according to a recent meta-analysis (pooled sensitivity 82% and specificity 94%), its presumed limited availability and further statistical confirmation is required for its being included in diagnosis.

If idiopathic AP, after negative routine work-up, endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) is advised identify rare morphologic abnormalities, if EUS is negative. If etiology remains unidentified, especially after a second attack of idiopathic pancreatitis, genetic testing may be considered.

TREATMENT

About 70% of patients with AP have mild pancreatitis as per revised Atlanta classification and most of them will respond to symptomatic medical treatment. These patients can be considered for early discharge from hospital once etiological workup is done and pain is better. Most patients with moderate pancreatitis can also be followed up on similar lines. However, patients with severe pancreatitis

by mansdocs.com

Table 4: Meta-analysis of studies comparing enteral nutrition (EN) with parenteral nutrition (PN) in AP.

Year	*Author*	*No. of RCT*	*Severity*	*Outcomes*
2006	McCabe et al.	27	Severe	• Decreased infectious mortality • Decreased hospital stay • No effect on organ failure
2008	Petrov et al.	15	Severe	• Decreased infectious complications • Decreased mortality, not significant
2008	Petrov et al.	5	Severe	• Decreased infections • Decreased mortality • Decreased organ failure, not significant

are likely to experience prolonged illness and have significant morbidity and in-hospital mortality. Presence of infected necrosis further worsens the prognosis in a patient with necrotizing AP. The management in these patients should be aggressive and broadly involves the following steps:

Fluid Resuscitation

Aggressive fluid resuscitation is the mainstay in the treatment of pancreatitis. Hypovolemia in pancreatitis occurs due to—vomiting, reduced oral intake, third spacing of fluids, increased respiratory losses and diaphoresis. Early aggressive intravenous fluid resuscitation provides micro- and macrocirculatory support to prevent serious complications such as pancreatic necrosis.

Although optimal infusion rates are difficult to determine most of the evidence suggests that the initial infusion rates of around 250–350 mL/h, especially in those of raised BUN and hematocrit. Careful planning should be done in the patients with concurrent renal, cardiac and systemic diseases. Aiming at a hematocrit greater than 35% within 48 hours had decreased rates of sepsis and mortality as compared to patients assigned to rapid hemodilution, aiming at a hematocrit less than 35% within 48 hours.

In a recent study, it was seen that administration of more than 4 liters of fluid during the initial 24 hours was associated with increased risk of respiratory insufficiency and a longer stay in the intensive care unit (ICU). Conversely, those who received less than 4 liters of intravenous fluid within the first 24 hours fared better—less of respiratory failure, less necrosis and lower mortality.

Assessing the response to fluid resuscitation:

- Noninvasive clinical targets of heart rate less than 120/min mean arterial pressure between 65 mm Hg and 85 mm Hg, and urinary output greater than 0.5–1 mL/kg/h
- Invasive clinical targets—central venous pressure (CVP)
- Biochemical targets of hematocrit 35–44%.

Nutritional Support

Acute pancreatitis is a hypercatabolic state and prompt and adequate nutrition is very essential. Enteral nutrition had been shown to be superior to the parenteral nutrition (Table 4).

In mild AP, oral intake is started early (usually as pain decreases). Low–fat solid diet appears to be safe as compared to liquid/soft diet. Early refeeding also decreases hospital stay.

In patients with moderate-to-severe pancreatitis, begin nutritional support early in the course of management, as soon as stabilization of fluid and hemodynamic parameters permits; optimally, nasojejunal (NJ) feedings with a low-fat formulation should be initiated at admission.

Nasogastric feeding appears to be safe and well tolerated. Advantages—easier placement, less costly (NJ tube requires endoscopy or interventional radiologic placement). Only a small theoretical risk of aspiration is there.

Enteral nutrition in AP had been associated with significant reduction in the infectious complications, surgery and mortality. A meta-analysis showed that significant reduction in infectious complications (RR –0.47, $p<0.001$), need for surgery (RR 0.37, $p< 0.001$) and mortality (RR 0.32, $p < 0.03$) with the use of enteral nutrition in patients with severe AP.

Delays in initiating enteral nutrition in severe AP lead to prolonged ileus and chances for intolerance. A study of 102 patients showed that 92% of patients tolerated feeding when started within 2 days. However, if it was delayed to 5 days, tolerance decreased by 50% and if the delay was beyond 6 days, the tolerance to enteral nutrition came down to 0%.

by mansdocs.com

ANTIBIOTIC PROPHYLAXIS

Antibiotics prophylaxis in AP is controversial. Infected necrosis has significantly higher mortality rates than sterile pancreatic necrosis (mean—30% vs 8%). Antibiotics that have been shown to penetrate in the pancreatic necrosis include carbapenems, quinolones, metronidazole. According to a meta-analysis of 14 randomized controlled trials (RCTs), there is no evidence to support the routine use of antibiotic prophylaxis in patients with (predicted) severe AP. A recent Cochrane meta-analysis suggested a reduction in pancreatic infection in the subgroup of patients who received imipenem, but the authors concluded that more evidence is needed. Thus, at present use of antibiotics in sterile necrosis in severe AP is not recommended.

Selective gut decontamination has shown some benefits in preventing infectious complications, however larger trials are required. Use of probiotics is not recommended as it has shown to increase mortality and did not prevent infections.

Sterile Necrosis

The management of sterile necrosis is generally medical and many people will improve on symptomatic therapy. Indications for intervention (either radiological, endoscopical or surgical) in sterile necrotizing pancreatitis are:

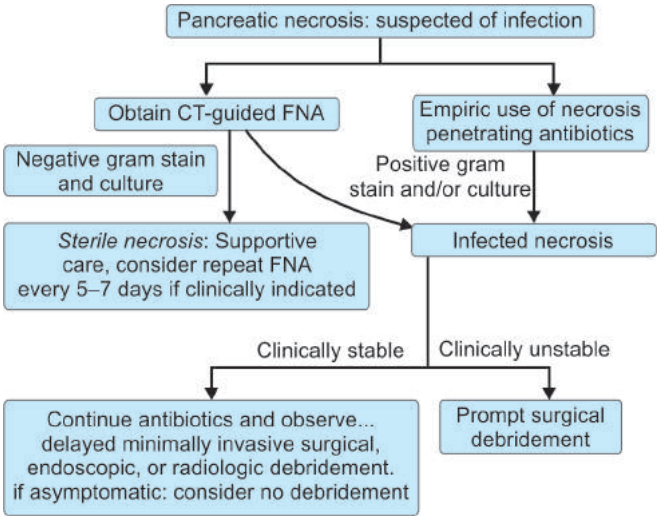
- Ongoing gastric outlet, intestinal or biliary obstruction due to mass effect of walled-off necrosis (i.e. arbitrarily > 4–8 weeks after onset of AP).
- Persistent symptoms (e.g. pain, "persistent unwellness") in patients with walled-off necrosis without signs of infection (i.e. arbitrarily > 8 weeks after onset of AP).
- Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily > 8 weeks after onset of AP).

Infected Necrosis

The approach to infected pancreatic necrosis is highlighted in Flowchart 1.

Rather than preventing infections now the target is to treat established infections. Infected pancreatic necrosis, which was promptly send for surgical debridement or necrosectomy in past, now are treated more conservatively with antibiotics. A meta-analysis of eight studies involving 409 patients with infected necrosis of whom 324 were successfully treated with antibiotics alone. Overall, 64% of the patients with infected necrosis in this meta-analysis could be managed by conservative antibiotic treatment with 12% mortality, and only 26% underwent surgery.

Flowchart 1: Approach to pancreatic necrosis.



Around one-third of necrotic AP may get infected by the 2nd week of severe AP. This complication should be suspected if a systemic inflammatory response persists for more than 2 weeks after admission, clinical course worsens or air bubbles appear at CT. These patients require either an ultrasound-guided or CT-guided fine-needle aspiration cytology (FNAC) from the tissue to confirm infected necrosis. However, it is not possible in all patients to obtain (Fine needle aspiration). Flowchart 1 can be used as a guide in management of infected necrosis.

In stable patients with infected necrosis, surgical, radiologic and/or endoscopic drainage should be delayed by preferably 4 weeks to allow the development of a wall around the necrosis (walled-off pancreatic necrosis).

In an unstable patients, minimally invasive approaches like radiologic catheter drainage, endoscopic transluminal drainage followed by (if required) endoscopic or surgical debridement is increasingly becoming the treatment of choice. It is prudent to mention that each patient should be individualized and the best time to have any kind of intervention is when the process had become walled off, i.e. after 4 weeks. Currently, a multidisciplinary consensus favors minimally invasive methods over open surgery for the management of pancreatic necrosis.

by mansdocs.com

ERCP IN ACUTE PANCREATITIS

The following recommendations are made by American College of Gastroenterology:

- Patients with AP and concurrent acute cholangitis should undergo ERCP within 24 hours of admission
- ERCP is not needed early in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction. In the absence of cholangitis and/or jaundice, MRCP or EUS rather than diagnostic ERCP should be used to screen for choledocholithiasis if highly suspected
- Pancreatic duct stents and/or postprocedure rectal nonsteroidal anti-inflammatory drug (NSAID) suppositories, recently indomethacin suppositories, should be utilized to lower the risk of severe post-ERCP pancreatitis in high-risk patients.

CHOLECYSTECTOMY

For Mild Biliary Pancreatitis

Cholecystectomy during admission appears safe and is recommended. Interval cholecystectomy is associated with substantial risk of readmission for recurrent biliary complaints. In a unfit elderly, one could refrain from cholecystectomy and endoscopic sphincterotomy could decrease rate of recurrent biliary pancreatitis, however usually do not prevent recurrent biliary colics and cholecystitis.

For Severe Biliary Pancreatitis

Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely. A retrospective study of 151 patients found an increased incidence of infected collections in patients who underwent early cholecystectomy after severe pancreatitis. Second retrospective study of 30 patients reported no episodes of recurrent biliary pancreatitis during the waiting period for interval cholecystectomy after routine ERCP and sphincterotomy.

Newer, Unproven Drugs

Protease inhibitors such as gabexate and camostat, anticytokines such as lexipafant and antisecretory agents like somatostatin or octreotide have been shown to decrease the severity of AP in occasional uncontrolled studies. Similarly, some Chinese medicines have been touted as being very effective in treating AP. However, none of them can be recommended as an accepted mode of therapy.

CONCLUSION

Acute pancreatitis can be severe in about 25% of the patients. Early, expectant medical management including aggressive fluid resuscitation and organ support is required in patients with severe pancreatitis. Minimally invasive techniques like subcutaneous drainage and minimally invasive surgery are sufficient in majority of patients with infected necrosis. Surgery may be required in a minority of patients who do not respond to less invasive modalities. The overall outcomes are excellent in patients with mild-to-moderate pancreatitis, but severe pancreatitis is still associated with significant mortality and morbidity despite advances in medical therapy.

BIBLIOGRAPHY

1. Ammann RW. The natural history of alcoholic chronic pancreatitis. Intern Med. 2001;40:368-75.
2. Andriulli A, Forlano R, Napolitano G, et al. Pancreatic duct stents in the prophylaxis of pancreatic damage after endoscopic retrograde cholangiopancreatography: a systematic analysis of benefits and associated risks. Digestion. 2007; 75:156-63.
3. Arguedas MR, Dupont AW, Wilcox CM. Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model. Am J Gastroenterol. 2001;96:2892-9.
4. Babu RY, Gupta R, Kang M, et al. Predictors of surgery in patients with severe acute pancreatitis managed by the step-up approach. Ann Surg. 2013;257:737-50.
5. Bakker OJ, van Santvoort HC, Hagenaars JC, et al. Timing of cholecystectomy after mild biliary pancreatitis. Br J Surg. 2011;98(10):1446-54.
6. Bakker OJ, Van Santvoort HC, van BS, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307: 1053-61.
7. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990;174(2):331-6.
8. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and defintions by international consensus. Gut. 2012;62:102-11.
9. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379-400.
10. Beck WC, Bhutani MS, Raju GS, et al. Surgical management of late sequelae in survivors of an episode of acute necrotizing pancreatitis. J Am Coll Surg. 2012;214:682-8.

by mansdocs.com

11. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371:651-9.
12. Bollen TL, Singh VK, Maurer R, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. Am J Gastroenterol. 2012;107:612-9.
13. Chang K, Lu W, Zhang K, et al. Rapid urinary trypsinogen-2 test in the early diagnosis of acute pancreatitis: a meta-analysis. Clin Biochem. 2012;45:1051-6.
14. Cravo M, Camillo ME, Marques A, et al. Early tube feeding in acute pancreatitis: a prospective study. Clin Nutr. 1989;8:14.
15. Das A, Singh P, Sivak MV Jr, et al. Pancreatic-stent placement for prevention of post-ERCP pancreatitis: a costeffectiveness analysis. Gastrointest Endosc. 2007;65:960-8.
16. de-Madaria E, Soler-Sala G, Sanchez-Paya J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. Am J Gastroenterol. 2011;106: 1843-50.
17. Dubner H, Steinberg W, Hill M, et al. Infected pancreatic necrosis and peripancreatic fluid collections: serendipitous response to antibiotics and medical therapy in three patients. Pancreas. 1996;12:298-302.
18. Eckerwall GE, Tingstedt BB, Bergenzaun PE, et al. Immediate oral feeding in patients with acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. Clin Nutr. 2007;26:758-63.
19. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366:1414-22.
20. Fernandez-del Castillo C, Rattner DW, Makary MA, et al. Debridement and closed packing for the treatment of necrotizing pancreatitis. Ann Surg. 1998;228:676-84.
21. Fleszler F, Friedenberg F, Krevsky B, et al. Abdominal computed tomography prolongs length of stay and is frequently unnecessary in the evaluation of acute pancreatitis. Am J Med Sci. 2003;325:251-5.
22. Freeman MF, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis. Summary of a multidisciplinary consensus conference. Pancreas. 2012;8: 1176–94.
23. Gardner TB, Coelho-Prabhu N, Gordon SR, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718-26.
24. Gardner TB, Vege SS, Chari ST, et al. Lack of aggressive fluid resuscitation is associated with organ failure in acute pancreatitis (abstract). Gastroenterology. 2008;134 Suppl 1): A373.
25. Gardner TB, Vege SS, Pearson RK, et al. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol. 2008;6: 1070-6.
26. Garg PK, Sharma M, Madan K, et al. Primary conservative treatment results in mortality comparable to surgery in patients with infected pancreatic necrosis. Clin Gastroenterol Hepatol. 2010;8:1089-94.
27. Heider TR, Brown A, Grimm IS, et al. Endoscopic sphincterotomy permits interval laparoscopic cholecystectomy in patients with moderately severe gallstone pancreatitis. J Gastrointest Surg. 2006;10:1-5.
28. Imrie CW. Prognostic indicators in acute pancreatitis. Can J Gastroenterol. 2003;17(5):325-8.
29. Jacobson BC, Vander Vliet MB, Hughes MD, et al. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. Clin Gastroenterol Hepatol. 2007;5:946-51.
30. Johnson C, Lévy P. Detection of gallstones in acute pancreatitis: when and how? Pancreatology. 2010;10:27-32.
31. Khoshbaten M, Khorram H, Madad L, et al. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 2008; 23:11-6.
32. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
33. Lankisch PG, Weber-Dany B, Hebel K, et al. The harmless acute pancreatitis score: a clinical algorithm for rapid initial stratification of nonsevere disease. Clin Gastroenterol Hepatol. 2009;7:702-5.
34. Leveau P, Wang X, Sun Z, et al. Severity of pancreatitis-associated gut barrier dysfunction is reduced following treatment with the PAF inhibitor lexipafant. Biochem Pharmacol. 2005;69(9):1325-31.
35. London NJ, Leese T, Lavelle JM, et al. Rapid-bolus contrast-enhanced dynamic computed tomography in acute pancreatitis: a prospective study. Br J Surg. 1991;78(12):1452-6.
36. Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. Curr Gastroenterol Rep. 2009;11:97-103.
37. Luiten EJ, Hop WC, Lange JF, et al. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg. 1995;222:57-65.
38. Mao EQ, Fei J, Peng YB, et al. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl). 2010;123:1639-44.
39. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23:1638-52.
40. McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. Cochrane Database Syst Rev. 2007:CD006233.
41. Moretti A, Papi C, Aratari A, et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. Div Liver Dis. 2008;40:379-85.
42. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? Pancreas. 2010;39(1):5-8.
43. Mortele KJ, Ip IK, Wu BU, et al. Acute pancreatitis: imaging utilization practices in an urban teaching hospital: analysis of trends with assessment of independent predictors in correlation with patient outcomes. Radiology. 2011;258:174-81.

by mansdocs.com

44. Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. Gastroenterology. 2013;144:333-40.
45. Nealon WH, Bawduniak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. Ann Surg. 2004;239: 741-9.
46. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg. 2006;23: 336-45.
47. Petrov MS, van Santvoort HC, Besselink MG, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomized trials. Arch Surg. 2008;143: 1111-7.
48. Raraty MG, Halloran CM, Dodd S, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. Ann Surg. 2010;251:787-93.
49. Rebours V, Vullierme MP, Hentic O, et al. Smoking and the course of recurrent acute and chronic alcoholic pancreatitis: a dose-dependent relationship. Pancreas. 2012;41: 1219-24.
50. Rodriguez JR, Razo AO, Targarona J, et al. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg. 2008;247:294-9.
51. Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: non-surgical treatment of infected necrosis. Pancreas. 2005;30:195-9.
52. Singh N, Sharma B, Sharma M, et al. Evaluation of early enteral feeding through nasogastric and nasojejunal tube in severe acute pancreatitis. A non-inferiority randomized controlled trial. Pancreas. 2012;41:153-9.
53. Spanier BW, Nio Y, van der Hulst RW, et al. Practice and yield of early CT scan in acute pancreatitis: a Dutch Observational Multicenter Study. Pancreatology. 2010;10:222-8.
54. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med. 1994;330:1198-210.
55. Talukdar R, Swaroop Vege S. Early management of severe acute pancreatitis. Curr Gastroenterol Rep. 2011;13:123-30.
56. Talukdar R, Vege SS. Recent developments in acute pancreatitis. Clin Gastroenterol Hepatol. 2009;7:S3-9.
57. Tenner S. Initial management of acute pancreatitis: critical decisions during the first 72 hours. Am J Gastroenterol. 2004;99:2489-94.
58. Van Baal MC, Besselink MG, Bakker OJ, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg. 2012;255:860-6.
59. Van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491-502.
60. Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev. 2006;(4):CD002941.
61. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. Gastrointest Endosc. 2006;63:1037-45.
62. Wittau M, Mayer B, Scheele J, et al. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. Scand J Gastroenterol. 2011;46(3):261-70.
63. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57:1698-703.
64. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252-61.
65. Yadav D, O' Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012;107:1096-103.
66. Zhang MJ, Zhang GL, Yuan WB, et al. Treatment of abdominal compartment syndrome in severe acute pancreatitis patients with traditional Chinese medicine. World J Gastroenterol. 2008;14(22):3574-8.

by mansdocs.com

CHAPTER

27

Hepatorenal and Hepatopulmonary Syndromes

Rajesh Pande

HEPATORENAL SYNDROME

It is functional renal failure with absence of histological changes that occurs in patients with chronic liver disease. It is generally seen in patients with progressive liver failure and ascites. Hepatorenal syndrome (HRS) can also occur acutely in certain settings like spontaneous bacterial peritonitis (SBP) and large volume paracentesis without albumin. There is marked renal vasoconstriction with reduction in the glomerular filtration rate (GFR).

DEFINITION

Hepatorenal syndrome can be defined as a unique potentially reversible form of acute renal failure (ARF) secondary to renal vasoconstriction that results from extreme vasodilatation. It is a functional disorder with no structural damage.

The general causes of acute kidney injury in patients with cirrhosis include acute tubular necrosis (41.7%), prerenal failure (38%), HRS (20%), post-renal failure (0.3%). In fact, cirrhosis is classified as described below.

Classification of the Cirrhotics

Type 1: Cirrhosis with rapidly progressive ARF
Type 2: Cirrhosis with subacute renal failure
Type 3: Cirrhosis with types 1 or 2 HRS superimposed on chronic kidney disease or acute renal injury
Type 4: Fulminant liver failure with HRS. The Child-Turcotte Pugh (CTP) classification based on the severity of cirrhosis is given in Table 1.

A Classical Case Presentation

A 44-year-old male with alcoholic liver cirrhosis-Child-Turcotte Pugh (CTP) class B gets admitted with pain abdomen and abdominal distension for last 7 days. He is febrile, icteric and has ascites, generalized abdominal tenderness and pedal edema. Investigations reveal a WBC count of 19,000/mL—90% polymorphonuclear cells; bilirubin is 2.5 mg%, serum glutamic oxaloacetic transaminase (SGOT) 108, serum glutamic-pyruvic transaminase (SGPT) 112, albumin 3 g %. Ascitic fluid shows 3,000 cells (85% polymorphs and 15% lymphocytes). Gram stain shows Gram-negative bacteria and *E. coli* is isolated from culture. His urea is 55 mg/dL and creatinine is 4 mg/dL. The final diagnosis is—Cirrhosis liver with portal hypertension (HTN) with ascites with SBP with raised creatinine.

The probability of HRS in patients with ascites:

- 20%—1-year probability
- 40%—5-years probability
- Highest in patients with more marked sodium and water retention and marked activation of vasoconstrictive systems.

HEPATORENAL SYNDROME

Hepatorenal syndrome is a severe complication of end stage liver disease associated with 80–95% mortality at 2 weeks (Fig. 1). The only interventions that have been shown to improve survival are liver transplantation and more recently the vasopressin analogs and transjugular intrahepatic portosystemic shunts (TIPS).

by mansdocs.com

Table 1: Child-Turcotte Pugh (CTP) classification of severity of cirrhosis.

	Points		
	1	*2*	*3*
Encephalopathy	None	Grade 1–2 (or precipitant-induced)	Grade 3–4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
PT (*see* prolonged) or INR	<4	4–6	>6
	<1.7	1.7–2.3	>2.3

CTP score is obtained by adding the score for each parameter
CTP class: A = 5–6 points
B = 7–9 points
C = 10–15 points
(PT: Prothrombin time; INR: International normalized ratio).

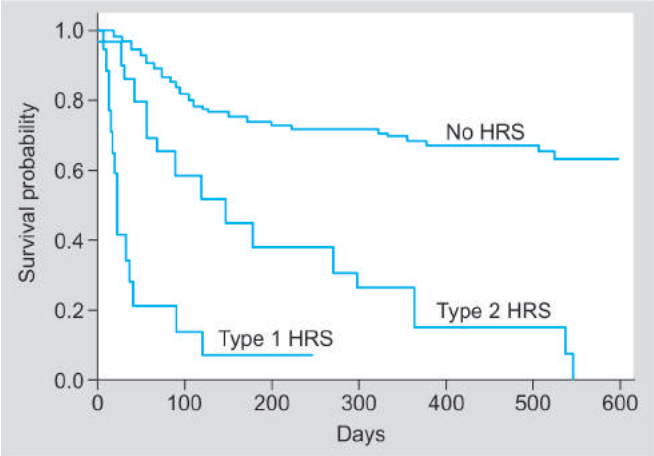


Fig. 1: Survival probability in hepatorenal syndrome (HRS).

Clinical Types of Hepatorenal Syndrome

Type 1 (Acute)

- Rapid decline in renal function
- Doubling of serum creatinine >132 (2.5 mg/dL) or reduction in 24 hours creatinine clearance to < 40 mL/min
- *Median survival*: Less than 2 weeks
- Seen in severe liver failure (jaundice, encephalopathy and spontaneous coagulopathy
- Associated with SBP (20%) or large volume paracentesis without albumin (15%).

Type 2 (Chronic)

- A less severe form of nonprogressive reduction in GFR
- Slower decline in renal function
- Associated with relatively preserved liver function
- Criteria for type 1 HRS not met
- Main clinical consequence is development of diuretic resistant or refractory ascites
- Median survival time is about 6 months.

Epidemiology

- *Incidence*: 7–10% in hospitalized cirrhotics with ascites, 20% at 1 year, 40% at 5 years
- Risk factors
  - Advanced ascites (diuretic resistant)
  - Large volume paracentesis without albumin (15%)
  - SBP (20%)
- Prognosis
  - Worst prognosis of all complications of cirrhosis
  - *Type 1 median survival*: < 2 weeks
  - *Type 2 median survival*: ~ 6 months
- Diagnosis is generally by exclusion as there are no specific tests.

Differential Diagnosis

- Differential diagnosis of renal failure in cirrhosis
  - Hypovolemia [gastrointestinal (GI) hemorrhage, shock]
  - Nephrotoxins (drugs, contrast)
  - Glomerulonephritis (Hepatitis B and C)
  - Acute tubular necrosis
  - Obstruction.

The differential diagnosis of renal failure in cirrhosis will also include drug-induced renal failure [aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs)], glomerulonephritis, sepsis, acute tubular necrosis, prerenal failure, etc. Acute tubular necrosis is characterized by abrupt impairment in function. The predisposing factors include hypovolemic or septic shock, or exposure to nephrotoxic drugs. The criteria that help in the diagnosis include increased urine sodium concentration, urine/serum osmolarity ratio and abnormal urine sediment. Glomerular disease is independent of etiology of cirrhosis and may manifest as proteinuria and/or hematuria. Prerenal azotemia is due to intravascular volume depletion (vomiting–diarrhea–diuretic overuse—shock). Unlike HRS,

by mansdocs.com

prerenal azotemia improves after plasma volume expansion with 1.5 L of isotonic saline.

Diagnostic Criteria

Major Criteria

International Ascites Club

- *Low GFR*: Serum creatinine greater than 1.5 mg/dL or 24 hours clearance lower than 40 mL/min
- Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs
- No sustained improvement in renal function (decrease in serum creatinine to less than or equal to1.5 mg/dL or increase in clearance to more than or equal to 40 mL/min) following diuretic with drawal and plasma volume expansion with albumin (or 1.5 L of isotonic saline)
- Proteinuria less than 500 mg/dL
- Absence of any evidence of obstructive uropathy or parenchymal disease as shown by ultrasonography.

Minor Criteria

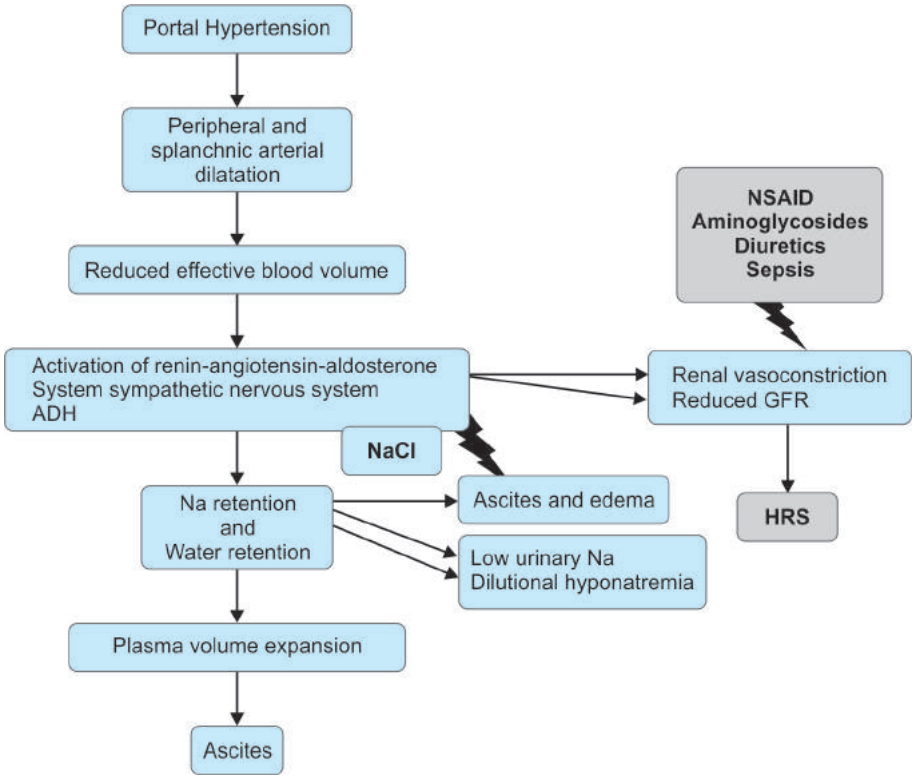
- Urine volume < 500 mL/day
- Urine sodium < 10 mEq/L
- Urine osmolality > plasma osmolality
- Urine RBCs < 50 per hpf
- Serum sodium < 130 mEq/L.

Pathophysiology

- *There is splanchnic arteriolar vasodilatation, which results in*:
  - Decreased effective arterial volume (EAV)
  - Decreased systemic vascular resistance
  - Hypotension
  - *Activation of vasoconstrictor systems*: Renin Angiotensin-Aldosterone-System, Sympathetic nervous system (SNS), Antidiuretic hormone.
- *There is hyperdynamic circulation, which results in*:
  - Hypotension from reduced effective arterial volume
  - Low systemic vascular resistance (SVR)
  - Baroreceptor activation
  - SNS activation leading to increased contractility
  - Increased cardiac output.

The development of HRS in cirrhotics is outlined in Flowchart 1. The role of vasopressin in chronic liver disease is highlighted in Flowchart 2.

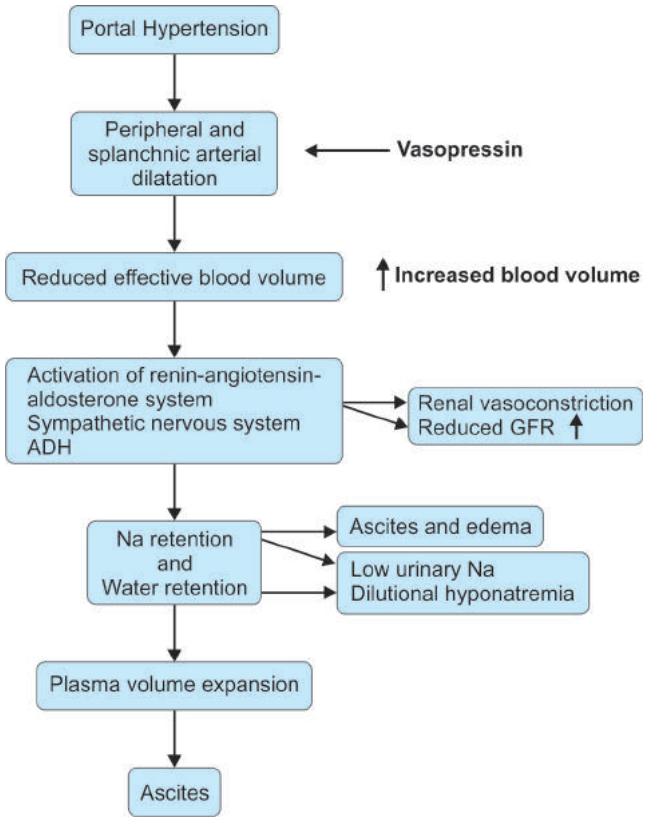
Flowchart 1: Pathophysiology of chronic liver disease.



(HRS: Hepatorenal syndrome; GFR: Glomerular filtration rate; ADH: Antidiuretic hormone).

by mansdocs.com

Flowchart 2: Role of vasopressin in chronic liver disease (CLD).



Treatment of Hepatorenal Syndrome

- Vasoconstrictors, often combined with albumin
- Vasopressin analogs (Terlipressin)
- Transjugular intrahepatic portosystemic shunt (Fig. 2)
- Liver transplantation.
- Improvement in renal function
  - Increased GFR postoperative versus decline in non-HRS patients
  - Lower overall GFR compared to non-HRS patients

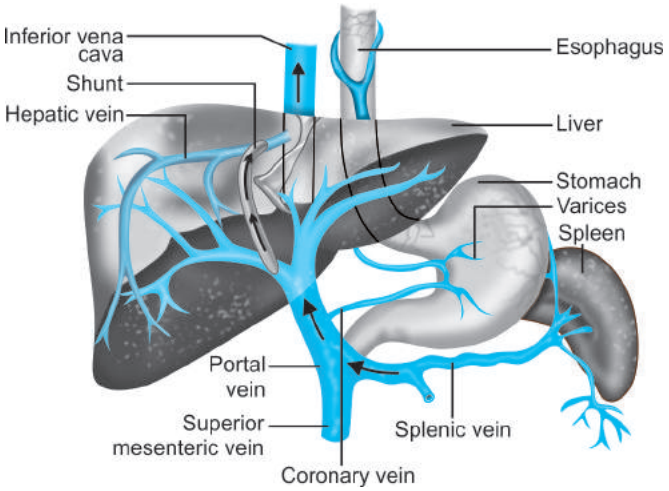


Fig. 2: Transjugular intrahepatic portosystemic shunt (TIPS).

Terlipressin

Terlipressin is a synthetic vasopressin analog and is the most studied drug for treatment of HRS. It is a V–1 receptor agonist and causes splanchnic vasoconstriction. The adverse events incidence is less than 5% and include arrhythmia and ischemia. It is given as an intravenous bolus.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

It reduces portal HTN and increases effective arterial volume with reversal of splanchnic vasodilatation. The complications include encephalopathy, shunt stenosis, hemolysis and hyperbilirubinemia.

Liver Transplantation

It is the treatment of choice for HRS. The limitations are organ availability and mortality of HRS. If the rate of complications is high, there is higher postoperative mortality, more days in the intensive care unit and increased need for postoperative requirement of renal replacement therapy (RRT) (35% vs 5% without HRS).

HEPATOPULMONARY SYNDROME

DEFINITION

Hepatopulmonary syndrome (HPS) is a disease process with a triad of: liver disease, evidence of widespread intrapulmonary vasodilatation and gas exchange abnormality—increased alveolar arterial oxygen gradient [ΔP (A–a) O_2] while breathing room air, resulting in hypoxemia.

The most common liver disease responsible for HPS is liver cirrhosis.

Other liver diseases may contribute:

- Noncirrhotic portal hypertension
- Extrahepatic portal vein obstruction
- Chronic active hepatitis
- Fulminant hepatic failure

by mansdocs.com

Table 2: Hepatopulmonary syndrome (HPS) versus portopulmonary hypertension (PPHTN).

	HPS	*PPHTN*
Pathophysiology	Arteriovenous (AV) shunting in the lung, predominantly at the bases. "Spider angiomata" in the lung	Similar to primary pulmonary hypertension with intense vasoconstriction of pulmonary capillaries as well as remodeled, thickened pulmonary vasculature
Symptoms	Platypnea	Dyspnea on exertion, syncope, orthopnea
Physical findings	Hypoxemia, orthodeoxia	Loud P2, RV heave, TR murmur, hypoxemia worsens with exercise (normal O_2 saturation at rest is common)
Echocardiogram	Positive bubble study	Elevated pulmonary artery systolic pressure
Treatment	Liver transplantation	Same as primary pulmonary hypertension; if mean PAP < 40 mm Hg, can safely undergo liver transplantation

(RV: Right ventricular; TR: Tricuspid regurgitation; PAP: Pulmonary artery pressure).

Prevalence of HPS ranges from 9% to 29% in patients with liver disease.

PATHOPHYSIOLOGY

The hypoxemia is due to wide spread pulmonary vasodilatation. The A–V communications result in direct R–L shunt of deoxygenated blood, pleural spider angiomas. The pulmonary capillary diameter may increase significantly. The persistent vasodilatation is explained by the imbalance of vasodilator and vasoconstrictors.This could be due to overproduction of the vasodilators from injured hepatobiliary system, decrease in their clearance by the liver, production of a vasoconstrictor inhibitor. The normal sensitivity of the pulmonary vessels to vasoconstrictors in response to hypoxemia is blunted in HPS. Various mediators involved in vasodilation include nitric oxide (NO), vasoactive peptide (VIP), calcitonin related peptide, glucagon, substance P and platelet activating factor.

Hypoxemia

The main issue is widespread pulmonary pre-capillary and capillary vasodilatation. Pulmonary capillary diameter is normally about 8–15 μm and this could rise up to 500 mm in HPS. In addition, there are distinct arteriovenous (AV) malformations and direct AV communications. Pleural spider angiomas may also form.

Hypoxemia due to ventilation perfusion (V/Q) mismatch is correctable by breathing 100% oxygen, whereas hypoxemia due to R–L shunting of blood is unresponsive to oxygen. Hypoxemia can also be due to diffusion impairment. There is excessive vasodilatation that causes O_2 molecules not to reach the center of dilated capillaries readily. The increased cardiac output and transition time of blood through pulmonary vascular bed further impairs diffusion.

Response to Breathing 100% O_2

If PaO_2 increases to levels 600 mm Hg, shunting of blood is unlikely. If it failed to exceed 500 mm Hg, shunt cannot be ruled out. If it did not rise to levels more than 150–200 mm Hg, shunt is most probably the main mechanism of hypoxemia.

Clinical Manifestations

Eight percent of cirrhotics manifest true clinical features of the hepatopulmonary syndrome (PaO_2 <60 mm Hg). The patient may be asymptomatic, or have dyspnea (only 18%), cyanosis, clubbing, platypnea (dyspnea improves on lying down), orthodeoxia. (hypoxemia improves on lying flat). Mortality is high 40%, within 2–3 years after presentation. Causes of mortality are most commonly nonrespiratory—GI bleeding, sepsis and renal failure.

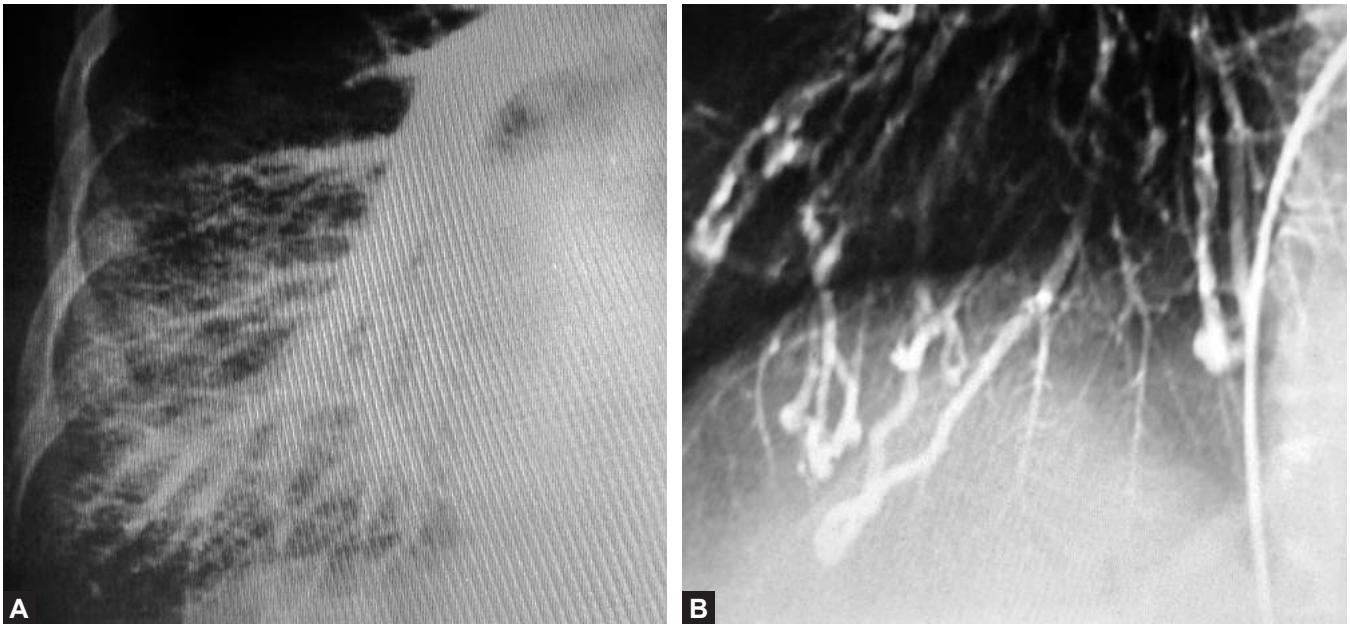
DIAGNOSIS

Diagnostic criteria for HPS are the presence of liver disease, and gas exchange abnormality manifested by hypoxemia (PaO_2 <70 mm Hg) and/or P (A–a) O_2 more than 20 mm Hg due to widespread intrapulmonary vasodilatation, in the absence of any primary cardiopulmonary disease. HPS needs to be differentiated from portopulmonary hypertension (Table 2).

Diagnostic Procedures

- *Arterial blood gas analysis*: Performed in the supine and sitting positions.
- *Chest X-ray and chest CT*: Are normal or show non-specific minor reticulonodular changes in the base of the lungs and/or dilatation of the peripheral pulmonary vasculature.

by mansdocs.com



Figs. 3A and B: (A) Type I: Dense spongy appearance; (B) Type II: Discrete arteriovenous fistula.

- *Pulmonary function tests*: Commonly show decreased diffusion ability of the lungs pointing to intrapulmonary vasodilatation.
- *Two dimensional contrast enhanced "bubble" echocardiography (CEEC)*: It is the method of choice for diagnosing intrapulmonary vasodilatation. An agitated saline solution (bubble 60–150 μm) is injected into a peripheral vein. Normally it is reabsorbed in pre-capillary vessels. In HPS, some of the bubbles are visible in the left side of heart (after 3–6 cardiac cycles). Delayed opacification is specific for intrapulmonary shunting. Transesophageal echocardiogram (TEE) may be better.
- *Macro aggregated albumin scanning*: Technetium 99m- labeled macro aggregated albumin is used. Normally they are lodged in pre-capillary vessels within the lung. In HPS, some particles get deposited in systemic microvascular bed. Whole body scan may detect these in brain and other organs.
- *Pulmonary angiography*: Two different angiographic patterns in HPS (Figs. 3A and B):
  Type I: More common. There are minimal changes with diffuse spider like branches to more advanced changes with a blotchy, spongy appearance (the type that responds to breathing 100% oxygen).
  Type II: Less common. There are vascular lesions as vascular dilatations representing A–V communications (responds poorly to breathing oxygen and liver transplantation is not suitable).
  The HPS diagnostic algorithm is given in the Flowchart 3.

TREATMENT

Medical Therapy

There are currently no medications proved to have persistent, adequate or acceptable effect on HPS. The following are tried: almitrine bimesylate is a stimulator of arterial chemoreceptors [used in chronic obstructive pulmonary disease (COPD)], indomethacin causes inhibition of prostaglandin production which has a putative role of vasodilatation. Methylene blue: It is a potent inhibitor of NO and its intracellular mediator, guanylate cyclase and is potentially effective for treatment of HPS although transiently. It might be used in the postoperative period of liver transplantation in cases with transient hypoxemia, however its routine and long-term use is not recommended yet.

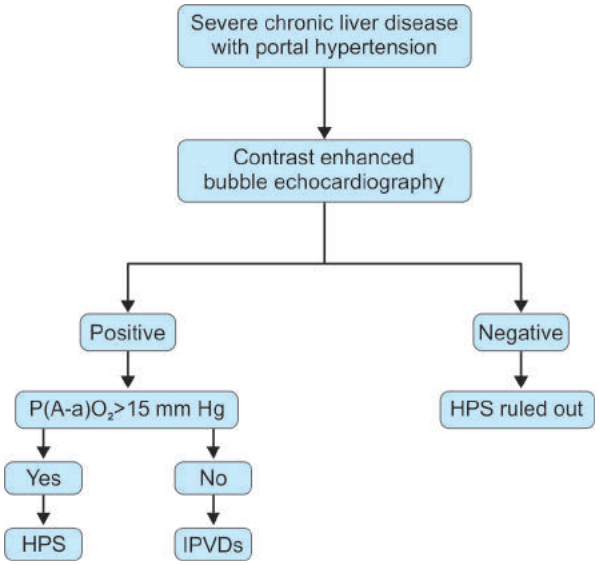
Interventions other Than Liver Transplantation

Embolotherapy

It is recommended that pulmonary angiography be done for HPS patients who respond poorly to breathing 100%

by mansdocs.com

Flowchart 3: Hepatopulmonary syndrome (HPS) diagnostic algorithm.



(IPVDs: Intrapulmonary vascular dilatations).

oxygen, i.e. PaO_2 < 150–200 mm Hg. If type II vascular lesions are diagnosed, embolotherapy with 22-coil spring devices must be tried.

Portal Decompression wtih Transjugular Intrahepatic Portosystemic Shunt

There is controversy regarding the beneficial effects of this technique on HPS. Some studies confirmed the improvement of hypoxemia and others ruled out any usefulness of TIPS. Probably more research studies are needed to clarify the issue further.

Orthotopic Liver Transplantation

It brings about resolution of disease, syndrome resolution in 62–82% patients. The normalization of abnormal oxygenation may take up to 15 months due to vascular remodeling. Refractory hypoxemia may be responsible for death. Post transplant recurrence is rare. The rate of improvement of HPS patients with type I vascular lesions undergoing orthotopic liver transplantation is about 80%, but is much less in those with type II lesions.

BIBLIOGRAPHY

Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;8(5):1151-7.

by mansdocs.com

CHAPTER

28

Anesthesia for Liver Transplantation

Vaibhav Kumar Nasa, Utpal Sarma, Amit Kumar Singhal

INTRODUCTION

Orthotopic liver transplantation (OLT) is the only definitive therapy for most forms of acute and chronic hepatic failure. The first successful orthotopic liver transplant was performed by Starzl in 1963. Since then, advances in surgical, anesthetic and immunological management have resulted in prolonged graft survival and overall 1 year survival rates are more than 80%. Liver transplantation is a complex surgical procedure which entails replacement of unhealthy liver with a new liver allograft. This surgical procedure is now widely common all over the world in various medical centers. However, the major limiting factors of this surgery is the lack of available donors. So, there is a rising trend in waiting list mortality which has led to a dramatic rise in the use of partial grafts from living donors, more frequent use of marginal or split livers from cadaveric donors and severity-based prioritization of recipients (Based on MELD score and PELD score). Thus, patients presenting for transplantation now have more advanced disease and receive grafts more likely to be challenging to implant than was the case a decade ago. So, all these trends demand more of the liver transplant anesthesiologist.

Because transplant procedure can challenge homeostasis in all major organ system and the association of liver failure with all other organ systems warrants a multidisciplinary evaluation of the patient involving a transplant hepatologist, anesthesiologist and transplant surgeon (Fig. 1).

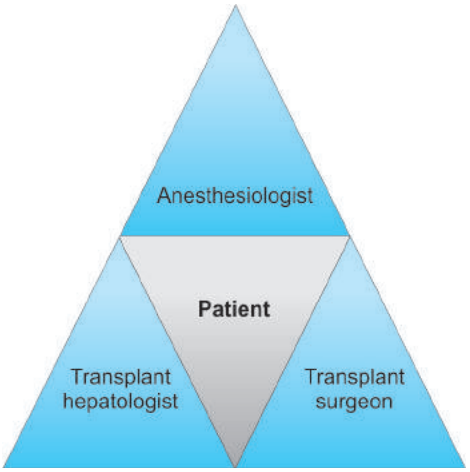


Fig. 1: Evaluation of a transplant patient.

The natural history of disease should be compared with the expected survival after liver transplantation. Current survival rates 1, 3, and 5 years after liver transplantation in the United States are 88%, 80%, and 75%, respectively. As a result, patients with a MELD (Model for End-stage Liver Disease) score of 15 or more and a CTP (Child-Turcotte-Pugh) score of 7 or more can be expected to achieve improved survival with liver transplantation.

Common indications for orthotropic liver transplantation are listed in Table 1.

In this chapter we have tried to focus on the disturbances common to all forms of advanced liver disease and on conditions that can be corrected to optimize the safety of the liver transplant patient.

by mansdocs.com

Table 1: Indications for orthotopic liver transplantation.

Cirrhotic diesease
- Virus-related cirrhosis
- Alcoholic cirrhosis
- Primary biliary cirrhosis
- Cryptogenic cirrhosis
- Autoimmune hepatitis

Cancers
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Biliary tract carcinoma
- Metastases

Cholestatic disease

Acute hepatic failure

Metabolic disease
- Wilson's disease
- Hemochromatosis

Other
- Budd-Chiari syndrome
- Benign liver tumors
- Failure of previous transplant (rejection, primary non-function)

Box 1: Evaluation protocol for live liver donor (followed at our center).

Phase I: Screening
- Blood group, Complete blood count, Liver function test, kidney function test, HCV Ab, HbsAg, HBcAb, PT, INR, APTT, Urine pregnancy test (UPT)
- Hepatitis B vaccination.
- Plain CT Scan Upper Abdomen for liver fat estimation with liver and spleen attenuation values in HU and LAI (liver attenuation index), MRCP.

Phase II
- Tri-phasic Liver CT Scan + Volumetry + Liver Angiogram.

Phase III
- Urinalysis, Serum Mg^2, Random blood sugar level
- *Endocrine profile*: Thyroid Function Tests, Lipid Profile.
- *Serology*: HIV I & II, CMV, IgG + IgM, VDRL, PPD (Mantoux test)
- Pulmonary function test (PFT), Chest X-Ray (PA view)
- ECG, Stress ECG
- For Female donors (married): Bilateral Mammography
  - USG, TVS, PAP Smear
- For Female donors (unmarried): USG breast

Phase IV
- Various consultations and clearances.

ANESTHETIC MANAGEMENT OF DONOR

Anesthetic Management of the Living Donors

We follow protocol based assessment of all the potential live liver donors (Box 1). We consider positive serology for hepatitis C as an absolute contraindication for living donation, even in the case of a recipient with hepatitis C cirrhosis. Donors with positive core antibody for hepatitis B at present are considered for hepatitis B infected recipients. These donors should have normal liver enzymes, normal liver histology and negative hepatitis B virus in serum detected by quantitative polymerase chain reaction assay. We consider a 20% or more degree of steatosis as an absolute contraindication for donation. In case of rates between 10% and 20% we recommend diet and the performance of a second biopsy after weight reduction. Results of 10% or less of fat infiltration are accepted.

In order to permit successful transplantation of the liver, it is necessary to provide excellent conditions for the donor while preserving optimal hemodynamic parameters to ensure donor safety.

Invasive monitoring is obligatory to ensure adequate organ perfusion. During the operation, the role of low central venous pressure (CVP) less than 5 cm H_2O is suggested in many liver transplantation protocols to decrease blood loss.

Balci et al. has recommended an acute normovolemic intraoperative hemodilution (ANIH) technique and fluid restriction in a group of live donors. But these measures are not free from risk such as postoperative renal failure and high morbidity. Intravenous fluid management involves administration of crystalloid for maintenance and blood loss up to a hematocrit level of 21% should be replaced by colloid preferably 5% albumin or 4% gelatin beyond this packed red cell should be used. Any coagulopathy should be detected promptly and managed with fresh frozen plasma (FFP) and cryoprecipitate administration.

Plan of anesthesia is general anesthesia along with epidural analgesia for postoperative pain relief. Commonly used anesthetic agents such as propofol for induction, fentanyl and/or morphine as analgesics, anesthesia is maintained by inhalational anesthetics preferably desflurane but isoflurane is also a safe alternative and muscle relaxation by atracurium or vecuronium infusion. In

by mansdocs.com

addition to venous thromboembolism prophylaxis including subcutaneous heparin or low-molecular weight heparin, pneumatic compression stockings should also be used. Prior to donor graft perfusion 3,000–5,000 IU intravenous heparin is administered and its reversal is often not needed.

Considering site and extent of incision epidural anesthesia seems to be effective and viable option. Incision congruent a mid-thoracic epidural catheter insertion may be the best form of pain relief during early postoperative period. However, despite the conflicting data that epidural analgesia seems to be unsafe in view of postoperative coagulation disorders in hepatectomy operations it has been used safely and recommended by other authors who have deployed thromboelastography (TEG) to assess coagulopathy in the postoperative period. Hwang and McCluskey reported that intravenous patient-controlled analgesia with morphine may become an alternative for pain control in living donors who refuse for epidural analgesia. Regional techniques such as paraspinal blocks, transverses abdominus plane blocks, and incisional field blocks are still investigated for their effect and safety in these patients.

Anesthetic Management of Brain-Dead Donors

Between 1990 and 2003 living donor liver transplantation (LDLT), accounted for only 3% of the total liver transplantations performed in Europe. In Eastern countries, including India the relation between LDLT and deceased donor liver transplantation is the opposite. The most extensive experience with LDLT is in Asia. In Korea, 985 LDLTs were performed between 2001 and 2003. In contrast, there were only 115 deceased donor liver transplantations during the same period. Situation is no better in India. Despite these low numbers anesthesiologist should be confident and well versed with the ICU management of brain-dead heart beating donors. Essentially donor management is a continuation of previous critical care management, but with a shift in goals of management. Problems encountered in such patients are listed in Table 2.

General management principles are aimed to maintain physiology close to normal values and were based on measurements made routinely in ICU patients. They included goals to maintain body temperature, ensure adequate oxygenation, circulating volume, cardiovascular stability, and adequate urine output (Table 3). An early, easily remembered series of goals was the "rule of 100": systolic arterial pressure 100 mm Hg, urine output 100 mL h^{-1}, PaO_2 100 mm Hg, hemoglobin concentration 100 g $liter^{-1}$. A later addition was blood sugar 100% normal.

Table 2: Incidence of common physiological derangements in brain-dead donors.

Derangement	*Cause*
Hypothermia	Hypothalamic damage; reduced metabolic rate; vasodilation and heat los
Hypotension	Vasoplegia; hypovolemia; reduced coronary blood flow; myocardial dysfunction
Diabetes insipidus	Posterior pituitary damage
Disseminated intravascular coagulation	Tissue factor release; coagulopathy
Arrhythmias	"Catecholamine storm"; myocardial damage; reduced coronary blood flow
Pulmonary edema	Acute blood volume diversion; capillary damage

ANESTHETIC MANAGEMENT OF THE RECIPIENTS

Once the patient is scheduled for liver transplantation, the transplantation team has to consider the deterioration in the recipient functional status. All members of team, especially anesthesiologists should do their best to reduce the morbidity and mortality of this procedure in such high risk patient population.

Preoperative Evaluation and Optimization

A detailed history, examination of each patient is followed by exhaustive laboratory investigations (Box 2). Problems are identified and their optimization holds the key for better outcome of such a lengthy and complex surgery.

Cardiorespiratory system: Since the criteria for transplantation is expanded, the age limits have been extended to the older ages, thus bringing ischemic heart diseases as a major problem to be evaluated in the preoperative period. Evidence suggests that coronary artery disease (CAD) is more prevalent in transplant candidates. Studies show that at least one critical coronary artery lesion occurs in 5–26% of all liver transplant candidates who are asymptomatic. A previous history or classic symptoms of CAD places patients in well-tested protocols that direct further evaluation. However, the challenge remains in

by mansdocs.com

Table 3: Summary of the principles of donor management.

	Suggested Approach
• General core	• Manage in ICU. Facilitates required nursing and medical care, and support for relatives. Minimum invasive cardiovascular monitoring includes arterial and central venous pressure. Cardiac output monitoring preferred. Review ICU therapeutic goals and alter to donor goals. Stop unnecessary drugs, e.g. sedatives. Reduce heat loss and actively warm if necessary to maintain core temperature > 35°C. Actively identify and treat any current infections. May require bronchoalveolar lavage (ling recruitment after)
• Respiratory	• Use "lung protective" ventilation. Tidal volume 6–8 mL/kg^{-1} with optimal PEEP to allow minimum FiO_2. Recruitment manoeuvres initially, and repeated after apnea testing or tracheal suction. Maintain tracheal cuff pressure at 25 cm H_2O and nurse with the head of the bed elevated to reduce the risk of aspiration. Avoid the administration of excessive IV fluids. Consider diuretics if marked fluid overload
• Cardiovascular	• Review fluid balance and correct hypovolemia; be aware that vascular tone may be impaired. Use cardiac output monitoring if possible to titrate fluids and inotropic or pressor drugs to intended goals as guided by retrieval team. If vasopressor drugs required, vasopression 0–2.4 units h^{-1} may reduce catecholamine requirements. High doses of catecholamines (e.g. norepinephrine > 0.05 μg/kg^{-1}/min^{-1}) should be avoided if possible. Consider triiodothyronine bolus and infusion
• Fluids and nutrition	• Administer maintenance fluids (can use enteral route), but avoid positive balance and hypernatremia. Monitor urine output and maintain at 0.5–2.5 mL/kg^{-1}/h^{-1}. If urine output is > 4 mL/kg^{-1}/h^{-1}, consider diagonsis of diabetes insipidus and treat with vasopressin infusion or DDAVP. Insulin infusion (1 unit/h^{-1} minimum) Maintain feeding or glucose source. Blood glucose target concentrations 4–8 mmol/liter^{-1}. Correct electrolyte abnormalities to normal values
• Blood and coagulation	• Correct coagulation if evidence of active bleeding; consider need for coagulation support during retrieval. Consider need for transfusion. Maintain thromboprophylaxis as there is a high incidence of pulmonary emboli found at retrieval
• Systemic effects	• Methylprednisolone 15 mg/kg^{-1} bolus immediately after brain death confirmed. Triiodothyronine
• Investigations	• (ECG: Echocardiogram). Coronary angiogram may be indicated. Bronchoscopy and lavage followed by lung recruitment manoeuvres. Chest X-ray after lung recruitment manoeuvres

Box 2: Preoperative laboratory investigation.

- Blood group and antibody screen, CBC, PT, APTT, fibrinogen, D-Dimer/FDP, PIVKA, LFT and KFT, BUN, Mg
- TIBC, serum Iron, ferritin, transferrin, HBA1c
- VDRL, HBsAg, HCV Ab, HBc Ab, HIV I/II
- CMV – IgG/IgM, VZV IgG/IgM, HSV 1 and 2, Mantoux test
- AFP, CEA, CA 19–9, PSA (For men), Ca 125 (For female pt.)
- SMA, AMA, ANA, P-ANCA, LKMA, serum ceruloplasmin (optional in-autoimmune/Wilsons disease)
- S. Copper, 24 hour urine copper, KF Ring (optional in-Wilsons disease)
- HCV – RNA qualitative
- HCV – RNA quantitative + Genotype (optional in-HCV related CLD)
- Hepatitis B vaccination
- HBV – DNA qualitative
- HBV – DNA quantitative (optional in-HBV related CLD)
- Thyroid profile, Lipid profile, FBS and PPBS
- Urine routine/microscopic,

Contd...

Contd...

- 24 hours. Urine for Na, protein, micro albumin creatinine and creatinine clearance
- Urine C/S, Blood C/S (Bact. Alert)
- PFT, ABG, Chest X ray
- ECG, Dobutamine stress ECHO (with RVSP and PVR values–TR Jet)
- For female patients (married): Bilateral mammography, USG TVS, PAP smear
- For female patients (unmarried): USG breast
- CECT [(Triphasic) Abdomen]

Clearances

  - Dental checkup
  - Hepatology clearance
  - Cardiac clearance
  - Pulmonology
  - Psychiatry clearance
  - Gynecology clearances for female

- HLA –T and B CROSS-MATCH
- HLA typing for organ transplant

by mansdocs.com

identifying those patients who are asymptomatic, but have significant CAD. Although coronary angiography is the gold standard for this assessment, considering the usage of radiographic nephrotoxic contrast in a patient group with a high-risk of renal dysfunction precludes the usage of this technique; leading to other screening methods such as transthoracic echocardiography in combination with a stress test. Exercise tests are not suitable for end-stage liver disease patients, because they cannot complete the test adequately. Thus, pharmacologic stress tests, stress echocardiography or myocardial perfusion scan have to be used instead.

Dobutamine stress echocardiography (DSE) in most but not all studies, seems to be an effective screening test for occult coronary disease in this setting. However, cardiac catheterization should be performed in patients with positive stress tests to confirm and to delineate further the extent of the coronary disease. It offers the added advantage of diagnosing pulmonary hypertension and valvular heart disease.

The circulatory dysfunction associated with advanced liver disease are summarized in Table 4.

Its etiopathogenesis can be explained by splanchnic vasodilatation mediated by increased NO generation in splanchnic vascular beds. In addition, vascular endothelial growth factor (VEGF) seems to stimulate angiogenesis and the development of portosystemic collaterals. CGRP (calcitonin gene-related peptide) and adrenomedullin are powerful vasodilating peptides, which are both elevated in cirrhosis, especially in patients with ascites and the hepatorenal syndrome.

Cirrhotic cardiomyopathy is characterized by an increase in cardiac output, blunted systolic contractile response to stress, diastolic dysfunction and electrophysiological abnormalities. Adverse events due to cirrhotic cardiomyopathy are not as well characterized, but evidence suggests that some cardiovascular complications during surgery and in the postoperative period are caused by an impaired response to physiological stress. A study has shown that patients were more likely to develop hepatorenal syndrome following an episode of spontaneous bacterial peritonitis, if they had findings suggestive of cirrhotic cardiomyopathy. In another study, the inability to reach 82% of the predicted heart rate following dobutamine administration was associated with an increased risk of cardiovascular complications up to 4 months following transplant surgery. Ironically most patients with cirrhotic cardiomyopathy are diagnosed once they develop signs or symptoms of heart failure. And appropriate tests to diagnose it when patients are still asymptomatic remain elusive.

Table 4: Circulatory changes in different vascular beds in cirrhosis.

Systemic circulation:
- Plasma volume ↑
- Total blood volume ↑
- Non-central blood volume ↑
- Central and arterial blood volume ↓ (→)
- Arterial blood pressure ↓ (→)
- Systemic vascular resistance ↓

Heart:
- Hear rate ↑
- Cardiac output ↑
- Left atrial volume ↑
- Left ventricular volume ↓ (↑)
- Left ventricular end-diastolic pressure →
- Total vascular compliance ↑
- Arterial compliance ↑

Hepatic and splanchnic circulation:
- Hepatic venous pressure gradient ↑
- Postsinusoidal resistance ↑

Renal circulation:
- Renal blood flow↓

Pulmonary circulation:
- Pulmonary blood flow ↑
- Pulmonary transit time ↓
- Pulmonary arterial pressure → ↑

↑ → ↓ denote: increased, unchanged, and decreased. Arrows in parentheses describe less typical changes.

Prentis et al. assessed the feasibility of preoperative sub maximal cardiopulmonary exercise testing (CPET) for determining the cardiopulmonary reserve in patients being assessed for liver transplantation and its potential for predicting 90-day post-transplant survival. The optimal anaerobic threshold (AT) level for survival was defined to be greater than 9.0 mL/minute/kg. They concluded that preoperative cardio respiratory reserve (as defined by CPET) was a sensitive and specific predictor of early survival after liver transplantation.

Portopulmonary hypertension (PPHTN) is an uncommon complication of cirrhosis and portal hypertension, and is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg with a nor-mal pulmonary capillary wedge pressure (<15 mm Hg) and an

by mansdocs.com

increase in calculated pulmonary vascular resistance of greater than 240 dynes.sec.cm^{-5}. PPHTN can be classified as mild (PAsys 35–44), moderate (PAsys 45–59) and severe (PAsys ≥ 60). PPHTN is seen in 2–4% of patients with cirrhosis. PPHTN is associated with increased perioperative mortality and right heart failure. A number of studies have found that mild pulmonary hypertension is not associated with an increased risk of liver transplantation. However, severe pulmonary hypertension is associated with high perioperative mortality and, if not successfully treated, is a contraindication to liver transplantation. Nevertheless, patients with severe pulmonary hypertension who have been successfully treated with medical therapy have undergone transplantation safely. In most of these patients, pulmonary hypertension gradually resolves within 4–6 months after transplantation and medical therapy can be discontinued. For detecting preoperative PPHTN transthoracic echocardiography may be reliable enough in experienced hands and patient whose PAsys greater than or equal to 50 should undergo right heart catheterization. One-third of patients with a PAsys greater than 50 mm Hg have a high flow state with normal pulmonary vascular resistance on catheterization.

The hepatopulmonary syndrome (HPS) consists of the clinical triad of chronic liver disease, arterial deoxygenation, and widespread intrapulmonary vasodilation. Preoperative evaluation of patients suspected of having HPS should include arterial blood pO_2 determination, transthoracic contrast echocardiography (gold standard), arterial oxygen response to 100% oxygen administration, and quantification of intrapulmonary shunting using a macroaggregated albumin (MAA) scan. Preoperative PaO_2 less than or equal to 50 mm Hg alone or in combination with a MAA shunt fraction of 20% or more are the strongest predictors of postoperative mortality. Because the condition is reversible after liver transplantation, HPS has become an indication for urgent transplantation. Patients with clinical evidence of HPS and PaO_2 of less than 60 mm Hg on room air with no underlying lung disease can receive enhanced prioritization for organ allocation. Most frequently these vascular abnormalities are limited to the capillaries and precapillaries (hepatopulmonary syndrome type I). In the most severe cases of hepatopulmonary syndrome (type II), there are also greater arteriovenous communications, and therefore these patients do not have a significant improvement in PaO_2 with high FiO_2. Other causes of hypoxemia, such as pleural effusion, ascites, pneumonia, emphysema, or pulmonary fibrosis, should be excluded.

Hepatic hydrothorax occurs in about 5–12% of patients with cirrhosis and portal hypertension. It is usually right sided. The etiology is most likely an anatomical defect in the hemi-diaphragm. Large pleural effusions result in severe dyspnoea, respiratory compromise, or even cardiac tamponade, and may require immediate intervention. A diagnostic thoracocentesis is required to exclude infection or another diagnosis (tuberculosis). Since the cause of the hydrothorax is usually the same as that of ascites, its management will be similar such as salt restriction, diuretics and repeated thoracocentesis. While a surgical correction of the diaphragmatic defect is rarely indicated. If refractory, a chemical pleurodesis should be considered.

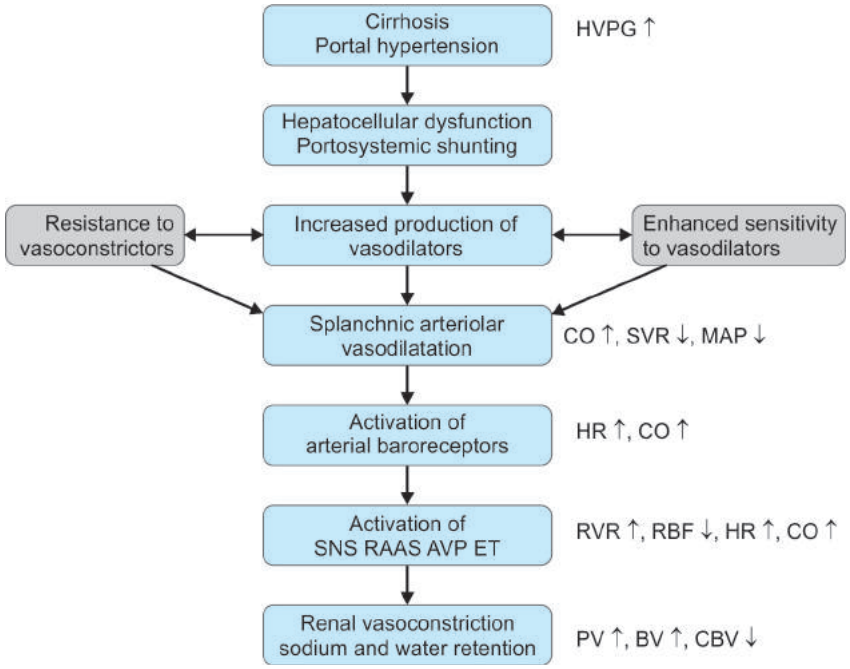
Ascites: Medical management of ascites includes low-salt diet, diuretics (e.g. spironolactone in combination with furosemide), and repeated paracentesis followed by colloid volume expansion. Transjugular intrahepatic portosystemic shunt (TIPS) has become an attractive alternative in refractory cases. Importantly, hyponatremia limits the diuretic therapy in patients with ascites. Large volume paracentesis should be attempted when patient is having respiratory embarrassment and/or intravesical pressure exceeds 25 mm Hg.

Renal system: Hepatorenal syndrome is a functional renal insufficiency or failure that occurs in patients with severe liver disease. The pathophysiology of hepatorenal syndrome: splanchnic vasodilatation, resulting in a reduction in SVR, which through activation of vasoconstrictor systems mechanisms leads to renal preglomerular vasoconstriction (Flowchart 1). Improvements in renal function before liver transplantation may improve the outcome of liver transplantation. Renal replacement therapy (hemofiltration or hemodialysis) does not seem to improve outcome, but recent studies indicate that the use of vasoconstrictors such as vasopressin analogues or a1-adrenoceptor agonists (e.g. norepinephrine) in combination with albumin administration may improve outcome.

Other renal protective measures have been investigated in many studies. Mannitol, furosemide and "low-dose" dopamine have been used in the hope of preventing intraoperative renal injury, without convincing evidence of a benefit. Steroids may also be beneficial, but are usually administered perioperatively as part of routine immunosuppression. Recently, the efficacy of fenoldopam (a selective DA-1 receptor agonist) has been investigated. Two randomized controlled trials have found some beneficial effects on postoperative creatinine concentrations and creatinine clearance, consistent with data

by mansdocs.com

Flowchart 1: Renal preglomerular vasoconstriction in hepatorenal syndrome.



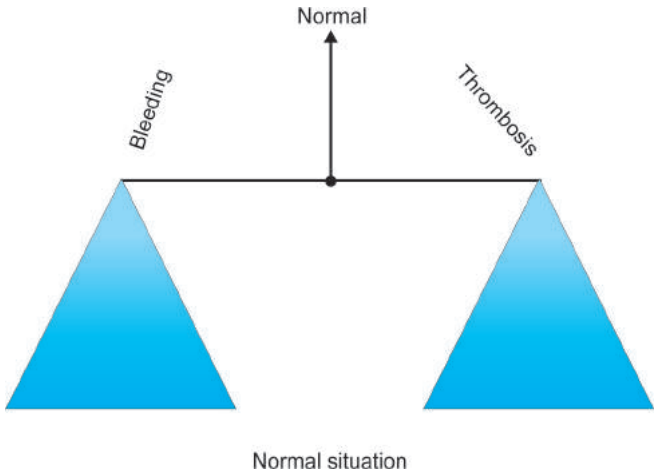


Fig. 2: Balance of coagulation.

obtained in other settings. The scope of both studies, however, was limited by the exclusion of patients with preoperative renal impairment, those most at risk of postoperative renal failure and mortality.

Hematological/Coagulation system: In physiologic conditions, the coagulation system is balanced by these two opposing drivers (Fig. 2).

Likewise chronic liver disease, particularly in the end stage, is characterized by decreased levels of most procoagulant factors, with the notable exceptions of factor VIII and von Willebrand factor, which are elevated and decreased levels of anticoagulants such as antithrombin and protein C. So the situation is somewhat comparable to normal hemostasis (Fig. 3).

Most importantly randomized clinical trials involving patients with chronic liver disease have shown that powerful procoagulant agents, such as recombinant activated factor VII, fail to control bleeding from the upper intestinal tract or bleeding during liver transplantation even though the prothrombin time is corrected considerably. So the validity of the prothrombin time test for assessing the risk of hemorrhage and guiding the transfusion of FFP in patients with chronic liver disease is questionable. Now it is believed that blood coagulation in such patients is rebalanced, owing to the parallel reduction of procoagulant and anticoagulant factors. Indeed, studies show that plasma from patients with cirrhosis generates as much thrombin (the final enzyme of coagulation) as plasma from healthy subjects, provided that thrombin is measured by methods that reflect the action of both procoagulant and anticoagulants. Thrombin generation is suppressed by thrombomodulin, a transmembrane protein situated on vascular endothelial cells which is a main physiologic activator of protein C. Plasma and reagents that are used to measure the prothrombin time do not contain thrombomodulin.

by mansdocs.com

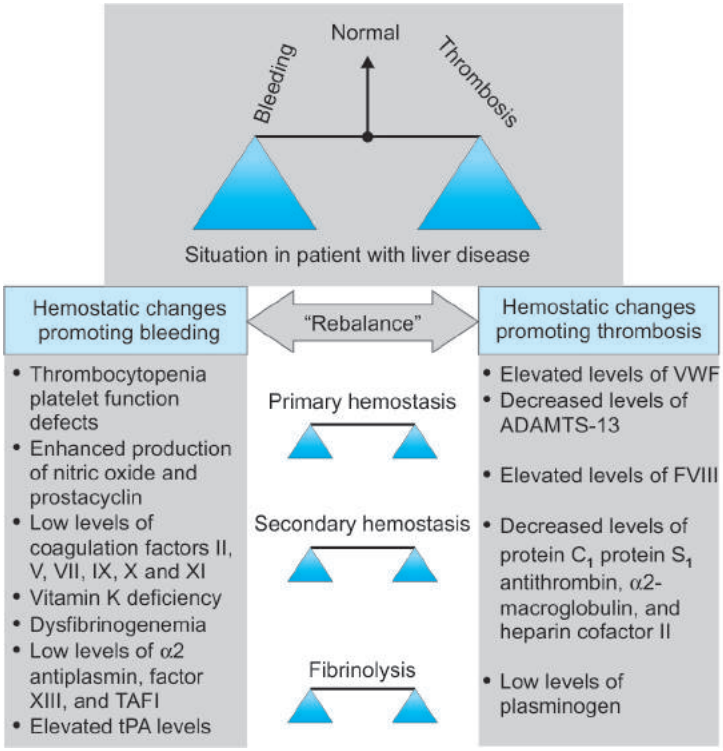


Fig. 3: Changes in homeostasis in chronic liver disease.

Accordingly, this test measures the amount of thrombin generated in plasma as a function of the procoagulant drivers, but not the thrombin inhibited by the anticoagulant drivers, especially protein C, which is not fully activated in the absence of thrombomodulin. This might explain why the prothrombin-time test and related tests do not truly represent the balance of coagulation in vivo and are inadequate for assessing the risk of hemorrhage in chronic liver disease patients.

Thus, the main culprits for the bleeding tendency observed in patients with end-stage liver disease should be sought among underlying conditions that favor hemorrhage, such as portal hypertension, endothelial dysfunction, bacterial infection, and renal failure. On the other hand, the restored balance of hemostasis afforded by the concomitant reduction of procoagulant and anticoagulant factors, together with increased levels of factor VIII, might explain why patients with chronic liver disease are prone for arterial and venous thrombosis. This apparent clinical paradox may be explained by the findings that these patients have a procoagulant imbalance in vitro owing to resistance to thrombomodulin and that their thrombocytopenia is compensated for by increased plasma levels of the adhesive protein von Willebrand factor.

Central nervous system: In advanced liver diseases, hepatic encephalopathy within a range of mild stupor, deep coma and unresponsiveness, is often seen. It is caused by substances generated in the intestines that normally are detoxified in the liver, which now bypass the liver and reach the systemic circulation. Diuretic therapy, hyponatremia, gastrointestinal bleeding, infections (spontaneous bacterial peritonitis) and advancement in liver disease worsen encephalopathy. In order to exclude a preexisting organic disease mimicking hepatic encephalopathy, EEG, and computed tomography are recommended to be performed. Conservative medical therapy includes a protein restricted diet, nonabsorbable disaccharides (lactulose), and nonabsorbable antibiotics (neomycin, metronidazole). Interestingly, recent evidence using neuropsychological tests indicates that minimal hepatic encephalopathy does not completely normalize after successful liver transplantation, suggesting that some of the changes in the brain may not be purely metabolic and may be irreversible.

Metabolic and electrolytes: Dilutional hyponatremia (serum Na < 130) occurs in approximately 20% of patients with decompensated cirrhosis and has been shown to be an independent predictor of death for patients with

by mansdocs.com

end-stage liver disease. Recent studies have shown that the risk of death is no worse in transplanted hyponatremic recipients but postoperative complications are still more likely. It has been suggested that correcting serum sodium values pretransplant may improve outcomes. The mainstay of pretransplant management of hyponatremia has revolved around water restriction and the withholding of diuretic therapy and this approach is often poorly tolerated by patients. Hypertonic saline is of limited efficacy and is associated with increasing edema and ascites. Albumin increases serum sodium in a small number of patients, perhaps as a result of restoration of circulatory volume and reversal of some of the AVP secretion associated with cirrhosis. O'Leary and Davis recently reported their experience with the use of conivaptan, a vasopressin-1 and V2 receptor antagonist that is administered intravenously and is approved by the Food and Drugs Administration (FDA) for the treatment of hypervolemic hyponatremia in hospitalized patients with normal liver function. Use of vaptans for the treatment of hyponatremia allows avoidance of fluid restriction, the continuation of natriuretic diuretics. Vaptans are presently not widely available nor approved by the FDA for use in patients with end stage liver disease.

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) issued a consensus statement on inpatient glycemic control in May 2009. Transplant patients were not specifically mentioned. Insulin therapy, preferably by infusion was recommended for critically ill patients when glucose exceeded 180 mg/dL, with a target range of 140–180 mg/dL. A retrospective study by Park et al. evaluated 680 adult patients who underwent OLT and specifically evaluated the risk factors for perioperative surgical site infections that occurred in 11.2% of their patients. Severe hyperglycemia, defined as a glucose greater than or equal to 200 mg/dL, was independently associated with postoperative surgical site infection. Hsaiky et al. presented their experience in 100 OLT recipients, and demonstrated a reduction in infection, rejection and mortality rates with the use of an intensive insulin therapy protocol.

Standard treatment module should be used for the treatment of hyper or hypokalemia, hypomagnesemia, and hypophosphatemia (particularly in alcoholics).

Intraoperative Management

Premedication: All patients should be considered to have full stomach; H2 receptor blockers plus prokinetic drugs and particulate-free antacids can be used preoperatively.

Monitoring: Routine monitoring ECG, oxygen saturations (SpO_2) and non-invasive blood pressure (NIBP) are established before induction. Further invasive cardiovascular monitoring may be established either pre- or post-induction depending on the cardiovascular stability of the patient. Capnography, nasogastric tube, urinary catheter and esophageal temperature probe are inserted. Patients at risk of raised intracranial pressure (ICP) (e.g. fulminant liver failure) are generally transferred from ICU with ICP monitoring in situ.

ECG: ECG monitoring is a cornerstone showing clinical outcome of electrolyte changes. Due to the rapid and profound changes in electrolyte levels during the various phases of liver transplantation, ECG may reflect the cardiac disturbances; which require prompt treatment. Fatal ventricular fibrillation due to the hyperkalemia during reperfusion period has also been reported.

Invasive blood pressure: Invasive arterial blood pressure monitoring is essential for providing continuous monitoring to see frequent hemodynamic changes usually secondary to surgical manipulations such as caval clamping, sudden blood loss, hepatic reperfusion during liver transplantation and also providing access for blood sampling for coagulation tests, blood gases analysis. Femoral arterial catheter is preferred over radial artery catheter by many, since central aortic pressure monitoring is considered more accurate especially at times of hemodynamic instability. Besides blood pressure monitoring using the radial artery is known to get affected by rib cage retraction causing subclavian artery compression. Therefore, both radial and femoral arterial catheters are used in some centers. If femoral arterial monitoring is not available, clinicians should rely on mean rather than systolic arterial pressure.

Cardiac output monitoring: One of the main overall hemodynamic goals is to maintain the high CO that is normally present in patients with advanced liver disease. Changes in arterial and venous tone, intravascular volume, ventricular performance, peripheral vascular reactivity, core body temperature and changes in blood rheology make moment-to-moment assessment of cardiovascular status difficult. Clinical parameters like heart rate, blood pressure, blood loss and urine output are sometimes insufficient to direct fluid therapy for a recipient of LT. More detailed and accurate measurements are therefore needed for assessing cardiac preload, directing volume replacement and optimizing CO. Traditionally, pulmonary artery catheter (PAC) has been used for invasive hemodynamic

by mansdocs.com

monitoring during LT. Cardiac filling pressures, namely central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP) measured using the PAC serve as a guide to right and left heart preload respectively. But recent studies have shown that these pressure-derived parameters, which are indirect indicators of ventricular filling volumes have little positive predictive value in improving hemodynamics or tissue perfusion. The PAC was initially used only to measure intracardiac pressures, but CO measurement using the thermodilution principle (TDCO) has now become an integral function of the PAC. Advances in technology have allowed for the development of continuous cardiac output (CCO) monitoring by incorporating a heating coil within the PAC (CCO combo/Vigilance, Edwards Lifesciences LLC, Irvine, CA; Opti Q CCO/Q-vue, Abbott Critical Care Systems, Mountain View, CA). This obviates the need for bolus injections and provides average CO over time compared with intermittent bolus techniques and still allows for monitoring of CVP, mean pulmonary artery pressure (mPAP) and PAOP. Advances in computation techniques have resulted in development of algorithms to calculate the global end-diastolic volume and the right ventricular end-diastolic (RVEDV) and end-systolic volumes, thereby facilitating better estimation of intravascular blood volume. RVEDV is a valuable index of cardiac preload and is a more sensitive indicator of intravascular volume when compared with CVP and PAOP. The PAC however, might be inaccurate if it is not positioned correctly and may not reflect changes in intravascular volume rapidly enough. With reported hazards of PAC insertion like ventricular arrhythmias, and due to availability of less invasive monitoring tools, the use of PAC is declining. It is now increasingly reserved, for those cases where there is a suspicion of PPHTN, as severe pulmonary hypertension (mPAP > 50) is associated with high perioperative mortality and, if not successfully treated, is a contraindication to LT.

Standard hemodynamic monitoring, such as arterial pressure monitoring, can also be extended for the assessment of CO, preload and afterload. A number of such devices are commercially available which provide a continuous estimate of CO through analysis of the shape of the arterial pulse wave from a peripherally placed arterial catheter. This technique helps to measure stroke volume (SV) and CO on a beat-to-beat basis and helps to assess requirement of therapies such as fluid challenge and/or inotropes. The PiCCO system (Pulsion Medical System; Munich, Germany) is a commercially available, continuous CO monitor in which a femoral arterial catheter with a thermistor in its wall analyses the pulse contour. The working principle is based on an algorithm which analyses the shape of the arterial pressure waveform and computes the pulsatile systolic area. Beat-to-beat calculations are averaged over 30-second cycles and are displayed as a numerical value providing information regarding the patient's preload [intrathoracic blood volume index (ITBVI)], afterload, myocardial contractility, CO and extra vascular lung water index (EVLWI). ITBVI has shown a strong correlation with cardiac index (CI) as opposed to filling pressures in cirrhotics. It is regarded as a more reliable preload index during different phases of LT like during IVC clamping, graft reperfusion, bleeding and surgical manipulations. The device is initially calibrated by TDCO, using cold saline injection via central venous catheter and subsequent detection by the thermistor in the femoral arterial catheter. Beat-to-beat calculations are averaged over 30-second cycles and displayed as a numerical value. CCO assessed by PICCO and by TDCO have been found to be comparable. The monitor however, needs to be recalibrated if the SVR changes markedly. Other popular commercial equipment that make use of pulse power analysis include the LiDCO plus (LiDCO Ltd; Cambridge, UK) and the FloTrac/Vigileo (Edwards Lifesciences LLC; Irvine, CA). Both devices use proprietary algorithms to derive CO and like PiCCO, both display pulse pressure variation and stroke volume variation, which are indicative of intravascular volume status. FloTrac/Vigileo derives CO from the arterial waveform in conjunction with patient demographic data, without the need for an independent method of calibration. CO can be measured directly from a conventional arterial line attached to the sensor. The LiDCO system needs to be calibrated using lithium dye. However, its advantage over other pulse contour derived methods is that it provides beat to beat changes in CO, while the Vigileo computes and displays SV values every 20 s. The values obtained from LiDCO and the FloTrac have been compared with PAC and found to be comparable. More recently transesophageal echocardiography (TEE) has become an essential perioperative diagnostic and monitoring tool. It provides direct visualization of the function and volume status of the heart. It allows quick assessment of the changes in contractility and rapid diagnosis of ventricular dilatation and failure. During times of hemodynamic instability, TEE can help with immediate diagnosis of air or thromboembolism. CO can be derived by measurement of flow across a cardiac valve, left ventricular outflow tract, or the flow in the main

by mansdocs.com

pulmonary artery. The functional utility of TEE, is however limited as a hemodynamic tool during LDLT due to the fear of rupture of esophageal varices but is considered a reliable, hemodynamic monitoring tool where there is adequate operator experience.

The preferred hemodynamic monitoring tool remains controversial because of lack of evidence indicating a difference in patient outcomes. Schumann surveyed 62 transplant centers in the United States and found that PACs were used in 30% of the centers and that TEE was used in 11.3%. In summary, the type of monitoring differs among transplant centers and is mainly determined by individual or institutional practice. In our centers, an arterial line is placed which is extended for CO monitoring using FloTrac (Fig. 4). The PAC is usually reserved for cases with suspected PPHTN. And the TEE is used as per availability of expertise.

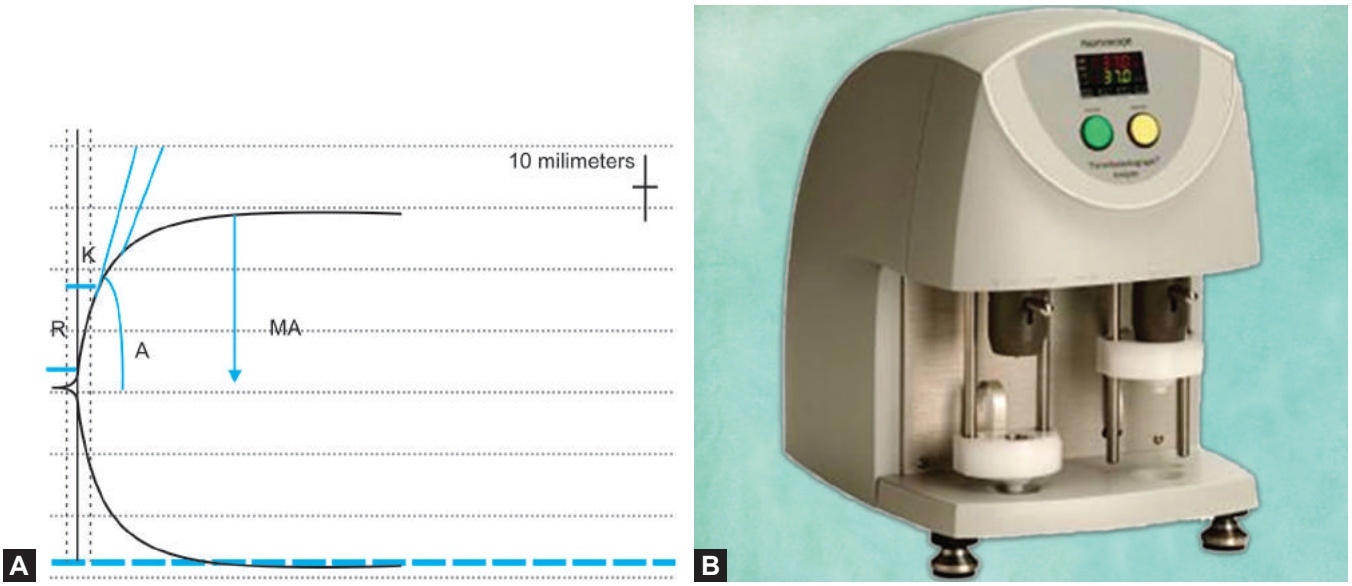


Fig. 4: Cardiac output monitoring by FloTrac.

Coagulation monitoring: During LT, dissection in the presence of coagulopathy through the fragile and dilated collaterals leads to blood loss. Transfusion needs in these patients may vary between 2 and 13 packed RBC units during liver transplant to much more. The inherent risk of use of blood products, along with scarcity of these resources, makes it important that these be used judiciously. Studies have linked intraoperative transfusions with significant decrease in 1-year survival and the amount of blood product administered intraoperatively has been a significant predictor of ICU readmission. There has been a consistent decline in transfusion requirements over the years with refinement of surgical technique and revision in transfusion protocols. The evaluation and correction of coagulopathy is an essential part of the care of the liver recipient in the perioperative period. It includes diagnosing potential causes of hemorrhage, prediction of risk of bleeding and appropriate hemostatic therapy. Close observation of the surgical field, suctions, communication with the surgical team along with monitoring of coagulation indices in the operating room are a crucial part of management. Traditionally, coagulation has been monitored by conventional coagulation tests (CCTs) which include prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count and plasma fibrinogen levels. Each of these measures a different aspect of the clotting process but even when put together, they may not provide a complete picture of the coagulation status and have a dubious role in guiding correction of coagulopathy in chronic liver disease patients prior to interventions as explained earlier in this chapter. Anesthesiologists and intensivists managing liver transplant patients usually use a combination of coagulation studies to guide blood product replacement therapy during LT. These include CCTs with point of care (POC) devices which assesses the viscoelastic properties of whole blood, like thromboelastography (TEG), rotation thromboelastometry (ROTEM) and Sonoclot to overcome the limitations of CCTs. These tests are repeated frequently during the surgery for correction of coagulopathy and reduce blood loss and transfusions.

Thromboelastography measures the elastic property of fibrin from its formation to complete dissolution is widely used to monitor coagulation status. The importance of TEG during LT as a test of whole-blood coagulation has been established in literature. The test allows for in vivo interactions between platelets, red blood cells and other coagulation factors and clot development is displayed in real-time. Rotation thromboelastometry (ROTEM) is another POC test. It is a variation of TEG and is based on measuring shear-elastic modules during clot formation in whole blood. TEG and ROTEM both measure and graphically display the changes in viscoelasticity of blood at all stages of the developing and resolving clot, i.e. the time until initial fibrin formation [reaction time (R)], the kinetics of fibrin formation and clot development [angle (a)], the ultimate strength and stability of the fibrin clot [maximum amplitude (MA)], and clot-lysis [fibrinolysis (CL)] (Fig. 6A). TEG and ROTEM are both fibrinolysis sensitive assays and allow for diagnosis of hyperfibrinolysis in bleeding patients and hence enable directed therapy. Literature shows that use of TEG and

by mansdocs.com



Figs. 5A and B: (A) Thromboelastograph (TEG) trace; (B) Thromboelastography (TEG) machine. (R: Reaction time; K: Kinetics; A: Slope between R & K; MA: Maximum amplitude; CL: Clot-lysis).

ROTEM in transfusion algorithms has led to reduced number of blood products transfused. ROTEM has been successfully used primarily in Europe. The reason for this disparity could be institutional availability and protocols. At our center we primarily use TEG. (Figs. 5A and B)

Temperature monitoring: PA catheter may be utilized for temperature monitoring or in its absence temperature probe is carefully inserted into the nasopharynx. Core body temperature is maintained to near normal (35–36°C) by using forced air warmer, heating mattresses, heating blankets, hot lines and rapid infuser system.

Anesthetic induction: An IV crystalloid infusion is commenced before induction and continued as maintenance fluid. Rapid sequence induction is followed. However main requirement of induction is cardiovascular stability. A variety of induction agents are used in different centers. Increasing interest in early extubation has led to the use of shorter-acting drug combinations, including midazolam, propofol and remifentanil, and rocuronium.

Maintenance of anesthesia: After intubation, IPPV is established with a suitable volatile agent, for example desflurane 4.0–6.5% end-tidal concentration in oxygen-enriched air. Desflurane has the advantage of a quick recovery time and low hepatic metabolism. Many centers use either isoflurane or sevoflurane successfully. Nitrous oxide is avoided to reduce cardiovascular depression, gut distension and bubble formation if on veno-venous bypass (VVB). Total IV anesthesia with propofol has been used successfully, but may be associated with cardiac depression after reperfusion. A remifentanil infusion (0.05–0.3 mg kg^{-1} min^{-1}) provides intraoperative analgesia with the advantage of a very short context-sensitive half-life. Alternatives include fentanyl infusion provided infusion is discontinued well in time. Muscle relaxation with atracurium (at 30 mg h^{-1}) provides adequate relaxation and reliable reversal after prolonged use. Most relaxants are safe provided neuromuscular block is monitored to prevent delayed recovery.

Intravenous fluids and blood products: Large bore cannulae are required for rapid transfusion of blood and fluids. A 3–5 lumen central line and 9FR advanced venous access (AVA) is inserted under ultrasound guidance. A rapid infusion system [(e.g. "Level-1") Fig. 6] allows rapid transfusion of warmed fluids (37–38°C) at rates of up to 1500 mL/min. FFP, colloid and electrolyte solutions are used with packed red cells to achieve a hematocrit of 0.26–0.32. FFP, cryoprecipitate and platelet infusions are administered if required according to measures of coagulopathy and clinical bleeding. The rationale for the target hematocrit is to allow adequate oxygen delivery but to prevent hepatic artery thrombosis. Monitoring of full blood count, clotting, electrolytes and blood gases is carried out hourly or as clinically indicated. This guides management of ventilation, calcium, potassium and magnesium supplementation, glycemia and acid-base management, and blood replacement therapy. Occasionally

by mansdocs.com

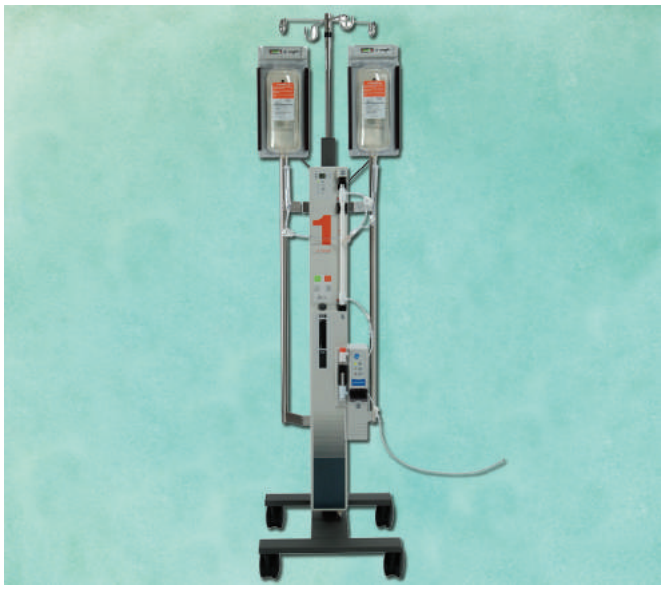


Fig. 6: Rapid infusion system.

10–50% dextrose may be required to treat hypoglycemia; this is more likely to occur in cases of severe acute liver failure.

Three Phases of Liver Transplantation

Surgery falls into three phases. Each of the three phases of liver transplantation poses particular problems for the anesthesiologist.

The pre-anhepatic phase: The surgical approach normally utilizes an inverse T or "Mercedes" incision. Dissection may be complicated by steady and sometimes rapid hemorrhage caused by varices in the abdominal wall or adhesions within the abdominal cavity. Fluid shifts and hemodynamic instability including ventricular arrhythmias may result from ascitic decompression during this phase. To prevent this 5% albumin is infused rapidly (8 gm/liter^{-1} of ascitic fluid drained). In addition Mesenteric traction syndrome can be seen during this stage; hypotension here is caused by a sudden and dramatic decrease in SVR, which is the result of the release of prostaglandins from the intestines in response to their surgical manipulation. Myocardial contractility can be affected by hypocalcemia, which is the result of calcium chelation through the citrate load with massive transfusion. Normally, citrate is metabolized by the liver and to a smaller degree by the kidneys; this process is significantly impaired in patients with severe liver disease. Also major acid-base abnormalities can lead to a decrease in myocardial contractility.

There is much interest recently in reducing central venous pressure to reduce blood loss in LT and in liver resection. These authors found that this technique was tolerated well, but others report an increased requirement for vasoactive drugs (phenylephrine and norepinephrine) and a higher rate of postoperative renal failure. Until these conflicting results are clarified, aggressively lowering of central venous pressure to reduce blood loss is not advised.

The anhepatic phase starts with the occlusion of blood inflow to the liver and ends with graft reperfusion. During the anhepatic phase, there is further physiological derangement. No hepatic clotting factors are produced, fibrinogen is deficient and anti-thrombin concentrations decrease, leading to worsening coagulopathy and the onset of fibrinolysis. Thrombocytopenia can develop owing to massive blood transfusion and platelet consumption, exacerbating preoperative thrombocytopenia. Fibrinolysis may be prevented or attenuated by antifibrinolytic agents, such as tranexamic acid. Absent citrate and lactate metabolism results in progressive acidosis. Hypocalcemia because of citrate accumulation is treated by slow IV calcium infusion. Ionized calcium should be maintained between 0.84 mmol/liter^{-1} and 1.4 mmol liter^{-1} to prevent coagulopathy and cardiac depression. Magnesium may also need to be supplemented. Cross-clamping of the inferior vena cava (IVC) and portal vein at hepatectomy produce a marked decrease in venous return, typically reducing cardiac output by 40–50% and arterial blood pressure by a variable amount. An extracorporeal circuit (venovenous bypass, VVBP) can be used to return blood from the infrahepatic IVC and splanchnic circulation to the right heart, which limits the fall in cardiac output to 20–30%, and usually maintains arterial pressure. Use of the "piggyback" (PGB) implantation technique, during which the IVC is side-clamped, sometimes with the addition of temporary portocaval shunting (PCS), is now much more common and also attenuates these changes. Some centers use VVBP in all adult patients, others use it selectively for given medical and surgical indications (such as severe portal hypertension, ALF with elevated ICP, renal impairment, hypotension on caval clamping), while some never use it, usually employing the PGB technique. At our center we use temporary PCS. Mannitol, with its potential for free radical scavenging and antioxidant properties, can help to remove free water in the abdominal organs, which is due to the congestion of blood flow through the fibrosed liver; particularly being useful in hepatorenal syndrome. Mannitol (0.3–0.5 g/kg^{-1}) can be used before

by mansdocs.com

clamping or during the anhepatic phase. Methylprednisolone (10 mg/kg^{-1}) is administered before reperfusion to protect against graft dysfunction and renal injury.

In neohepatic phase, when the venous anastomosis to the graft is completed, the liver is flushed with blood and the clamp on IVC is released. On reperfusion of the preserved liver there is a sudden massive release of cold, hyperkalemic, acidotic fluid into the circulation. $CaCl_2$ is given to prevent potassium related arrhythmias. Before reperfusion, methylprednisolone (10 mg/kg^{-1}) is also given as a slow IV infusion as immunosuppression and to protect against ischemia-reperfusion injury. There is a variable decrease in heart rate, contractility and peripheral vascular tone, often causing arterial hypotension and bradycardia. These are usually short lived, although sustained hypotension and a need for vasopressor support are seen in some patients. The latter was described as "post-reperfusion syndrome" (PRS) by Aggarwal et al. in 1987, and defined as at least 30% decrease in mean systemic blood pressure for more than 1 minute during the first 5 minute following graft reperfusion. These changes may be attenuated in the PGB technique and by initial reperfusion using the hepatic artery although initial portal revascularization is reported to result in better cardiac filling, higher arterial pressure and earlier normalization of lactate. Thus, initial arterial reperfusion of the graft results in a more gradual hemodynamic effect and may be appropriate in patients with poor cardiac reserve, while initial portal reperfusion would still be preferable in others. There is, however, no demonstrated impact on long-term outcome.

Early-extubation (Fast-tracking)

The concept of "fast-tracking", defined as immediate or very early postoperative tracheal extubation, was pioneered as a cost-saving measure in cardiac surgery and applied to selected OLT recipients from the mid-1990s. Those favoring the technique suggest that this approach might have beneficial effects on splanchnic and liver blood flow and reduce the risk of ventilator acquired pneumonia. Conservatives argue that a period of postoperative ventilation allows graft function to be consolidated with less sympathetic activation, and protects the patient from the risks of atelectasis, aspiration or reintubation for surgical re-exploration. In a recent series in which a fast-track anesthesia protocol was used, 75.5% of cases were successfully extubated very soon after completion of surgery and 56% were transferred directly to the ward, avoiding admission to the intensive care unit. A 13% reduction in total liver transplantation costs was reported. Another report however, found that although ventilation times could be reduced by a fast-track anesthetic technique, ICU length-of-stay was not. The introduction of the MELD-score based organ allocation system is likely to reduce the number of patients suitable for fast tracking. To date, no randomized study has confirmed that early extubation benefits the patient and reduces costs, and whether it should be a therapeutic goal remains debatable.

Postoperative Care

Monitoring in Postoperative Period

The principle behind institution of monitoring facilities for liver transplant patients in the postoperative period is to provide the necessary support for maintaining optimal function of all organ systems. All intraoperative modalities of monitoring and medication are continued into the ICU. This would help to provide a favorable milieu for the new liver to start functioning and at the same time would help in following the course of graft functioning.

Graft function is assessed at regular intervals by serial blood gas analysis, liver function tests and bedside ultrasound Doppler of hepatic vasculature. Improvement in metabolic acidosis, decline in blood lactate levels, and spontaneous improvement in INR are indicative of adequate graft uptake. Static and dynamic liver function tests are used to track graft function. Static tests of liver function include serum levels of liver enzymes, bilirubin and tests of synthetic function including serum level of albumin and coagulation factors. The dynamic liver function tests express the ability of the liver to metabolize or eliminate defined substances. The indocyanine green (ICG) clearance test is used in some centers routinely to quantify the functional activity of the graft. ICG is a water-soluble dye which can be used bedside or intraoperatively. Its removal from the blood depends on liver blood flow, parenchymal cellular function and biliary excretion. Other biochemical, hematological and microbiological monitoring is implemented depending on institutional protocols.

Postoperative Ventilatory Support

Patients who are not fit for extubation in the OR itself are electively mechanically ventilated for variable period of time provided they fulfil most of criteria for successful

by mansdocs.com

weaning. Some patients may require noninvasive ventilator (NIV) support for weaning. NIV by adding a pressure support (PS) with a continuous positive end expiratory pressure (PEEP) could prevent the loss of vital capacity and impede severe lung derecruitment following extubation. The first application of NIV in solid organ transplant recipients was described by Antonelli et al. They randomized patients with respiratory failure following transplantation to receive either NIV or standard therapy. Patients assigned to NIV showed a trend toward less ventilator associated pneumonia and a significant reduction of severe sepsis or septic shock episodes.

Pain Management

Patient-controlled analgesia or a morphine infusion is used for postoperative pain relief. Orthotopic liver transplant patients were reported to experience less pain and use less morphine in the postoperative period compared to liver resection patients. Chen et al. have found morphine consumption significantly lower in patients with end-stage liver disease undergoing living-donor liver transplantation; compared with healthy living liver donors, hepatocellular patients undergoing partial hepatic resection only on the first postoperative day.

Fluids and Blood Products

A rational approach to maintaining circulating volume is by providing two-thirds of required fluids with crystalloid and replacing half of drain losses with 5% albumin. Coagulation tests (TEG/ROTEM) and full blood count guide further transfusion of blood and blood products. The hematocrit is maintained between 0.26 and 0.32. Higher levels are associated with an increased incidence of hepatic artery thrombosis and graft failure.

Immunosuppression

There have been many recent advances in immunosuppressive drugs, but the most common protocols continue to consist of the calcineurin inhibitors associated with steroids. Cyclosporine achieves its effects through reversible inhibition of immunocompetent lymphocytes in the G^0 and G^1 phases of cell division. T-helper cells are the primary targets of the drug, although T-suppressor cells may be affected. Tacrolimus, like cyclosporine, suppresses humoral immunity through inhibition of B-lymphocyte activation. Tacrolimus also inhibits calcineurin which, in turn, results in decreased IL-2 production and dampening of T-cell recruitment and activation. However, O'Grady et al. and Kelly et al. demonstrated that the incidence of acute and steroid-resistant rejection was significantly lower with tacrolimus than with cyclosporine treatment.

Mycophenolate mofetil (MMF) has been used for years as an adjuvant immunosuppressive agent. It works by selectively inhibiting purine synthesis, and thus is a potent inhibitor of B and T-cell proliferation.

Corticosteroids are used routinely as part of the maintenance protocol for solid organ transplant recipients, and are the most important agents in the management of acute rejection. We at our center follow triple regimen comprising corticosteroids, tacrolimus, and MMF.

Infection Prophylaxis

Due to heavy immunosuppression the early postoperative period poses greater risks of infection. The source of the infecting organisms can be: (a) the donor organ and transfused blood products (b) the reactivation of previous infection (c) invasion by exogenous micro-organisms or by endogenous flora. Risk factors for VRE (vancomycin resistant enterococci) bacteremia include Roux-en-Y choledochojejunostomy, biliary strictures, prolonged ICU stay, and CMV infection. Treatment of bacterial infections generally involves characterization of the infective agent (e.g. cultures and antibiotic sensitivities), source control (e.g. catheter removal and debridement), and antibiotic regimens based on the hospital antimicrobial susceptibility patterns. Immunosuppression must be reduced or even halted temporarily. Prophylactic postoperative antibiotics are primarily tailored to Gram-negative (*Pseudomonas* sp*, Enterobacter* sp *and Klebsiella* sp) and Gram-positive organisms (*Staphylococcus aureus*). Prophylactic antifungal agents are used if predisposing factors for fungal infections such as preoperative renal dysfunction, fungal colonization at baseline, severity of end-stage cirrhosis, retransplantation, perioperative massive transfusion, need for extracorporeal renal assistance, prolonged ICU stay are present.

Nutrition

Energy requirements are only moderately elevated in the early period of uncomplicated LT. For this reason, some authors recommend that the caloric intake, determined by using the formulation provided by the Harris-Benedict equation, should be provided at approximately 120–130% of the calculated basal energy expenditure

by mansdocs.com

Table 5: Complications of early postoperative course.

Graft dysfunction	*Rejection*	*Vascular thrombosis*
• Primary nonfunction	• Hyperacute	• Hepatic artery thrombosis
• Preservation injury	• Acute	• Portal vien thrombosis
• Small for size syndrome		
Neurologic complications	*Biliary complications*	*Electrolyte disturbances*
• Encephalopathy	• Stricure	• Hyponatremia
• Seizure	• Leaks	• Hypocalcemia
• Coma	• Obstruction	• Hyperkalemia
• Psychosis	• Dilation	• Hypokalemia
• Aphasia		• Hypophospharemia
• Tremors		• Hypoglycemia
• Anoxic-ischemic events		• Hyperglycemia
• Central pontine myclinolysis		• Hypomagnesium
Gastrointestinal	*Drug interactions*	*Pneumonia*
• Ileus	• Interference with CYP3A4	• Renal dysfunction
• Ulcer		• Atelectasis
• Bleeding		• Infections
• Diarrhea		• Bleeding and coagulopathy

(BEE). As nitrogen loss is raised as a consequence of increased protein catabolism, liver transplant patients during the acute post-transplant phase should receive 1.5–2.0 g of protein per kilogram of dry weight. The potential persistence of postoperative encephalopathy does not require a reduction of protein content in the diet but only a change of amino acid composition in favor of BCCA-enriched formulae. Early postoperative nasoenteric tube feeding is preferred over total parenteral nutrition (TPN) unless a patient has a non-functional gastrointestinal tract or requires complete bowel rest. Although gastric and colonic ileus may be present following transplantation, early enteral nutrition is usually tolerated. Tube feeding results in decreased metabolic response to stress, fewer technical and metabolic problems, and enhanced visceral protein synthesis. Hasse et al. demonstrated that early enteral feeding prior to oral diet initiation was associated with significantly greater cumulative 12-day calorie and protein intakes than controls. In addition, results showed decreased rates of viral and bacterial infections and fewer infected patients in the tube-fed group than in the control group. Patients should be encouraged to start oral diets as soon as feasible although tube feeding should not be discontinued until patients are able to maintain an oral intake adequate to their nutrition requirements (at least 80% of normal nutritional need).

Postoperative Adverse Events

Despite substantial technological, medical and surgical advances, LT remains a complex procedure that is accompanied by significant morbidity. The most common complications of the early postoperative course are outlined in Table 5.

BIBLIOGRAPHY

1. Aggarwal S, Kang Y, Freeman JA, et al. Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. Transplant Proc. 1987;19:54-55.
2. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA. 2000;283:235-41.
3. Arguedas MR, Abrams GA, Krowka MJ, et al. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. Hepatology. 2003;37:192-7.
4. Balci ST, Pirat A, Torgay A, et al. Effect of restrictive fluid management and acute normovolemic intraoperative hemodilution on transfusion requirements during living donor hepatectomy. Transplant Proc. 2008;40:224-7.
5. Biais M, Nouette-Gaulain K, Cottenceau V, et al. Cardiac output measurement in patients undergoing liver transplantation: pulmonary artery catheter versus uncalibrated arterial pressure waveform analysis. Anesth Analg. 2008;106:1480-6.
6. Biancofiore G, Critchley LA, Lee A, et al. Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. Br J Anaesth. 2009;102:47-54.
7. Biancofiore G, Della Rocca G, Bindi L, et al. Use of fenoldopam to control renal dysfunction early after liver transplantation. Liver Transpl. 2004;10:986-92.
8. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology. 2004;127:1123-30.
9. Brienza N, Malcangi V, Dalfino L, et al. A comparison between fenoldopam and low-dose dopamine in early renal dysfunction of critically ill patients. Crit Care Med. 2006;34:707-14.
10. Buckels JA, Tisone G, Gunson BK, et al. Low haematocrit reduces hepatic artery thrombosis after liver transplantation. Transplant Proc. 1989;21:2460-1.

by mansdocs.com

11. Burtenshaw AJ, Isaac JL. The role of trans-oesophageal echocardiography for perioperative cardiovascular monitoring during orthotopic liver transplantation. Liver Transpl. 2006;12:1577-83.
12. Butler P, Israel L, Nusbacher J, et al. Blood transfusion in liver transplantation. Transfusion. 1985;25:120.
13. Button D, Weibel L, Reuthebuch O, et al. Clinical evaluation of the FloTrac/Vigileo system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. Br J Anaesth. 2007;99:329-36.
14. Cacciarelli TV, Keeffe EB, Moore DH, et al. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. Arch Surg. 1999;134:25.
15. Carey WD, Dumot JA, Pimentel RR, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. Transplantation. 1995;59:859-64.
16. Cerutti E, Stratta C, Romagnoli R, et al. Thromboelastogram monitoring in the perioperative period of hepatectomy for adult living liver donation. Liver Transpl. 2004;10:289-94.
17. Cheatham ML, Nelson LD, Chang MC, et al. Right ventricular end diastolic volume index as a predictor of preload status in patients on positive end expiratory pressure. Crit Care Med. 1998;26:1801-6.
18. Chen JP, Jawan B, Chen CL, et al. Comparison of postoperative morphine requirements in healthy living liver donors, patients with hepatocellular carcinoma undergoing partial hepatectomy, and liver transplant recipients.Transplant Proc. 2010;42(3):701-2.
19. Cho WH, Kim YS. Landmarks in clinical transplantation in Korea. Yonsei Med J. 2004;45:963-7.
20. Coakley M, Reddy K, Mackie I, et al. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth. 2006;20:548-53.
21. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology. 2003;37:401-9.
22. Costa MG, Chiarandini P, Della Rocca G. Hemodynamics during liver transplantation. Transpl Proc. 2007;39:1871-3.
23. Dahlbäck B. Progress in the understanding of the protein C anticoagulant pathway. Int J Hematol. 2004;79:109-16.
24. Dawwas MF, Lewsey JD, Neuberger JM, et al. The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study. Liver Transpl. 2007;13:1115-24.
25. de Boer MT, Molenaar IQ, Hendriks HG, et al. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. Dig Surg. 2005;22: 265-75.
26. Della Rocca G, Brondani Anita, Costa Maria Gabriella. Intraoperative hemodynamic monitoring during organ transplantation: what is new? Curr Opin Organ Transpl. 2009;14:291-6.
27. Della Rocca G, Costa MG, Coccia C, et al. Cardiac output monitoring: aortic transpulmonary thermodilution and pulse contour analysis agree with standard thermodilution methods in patients undergoing lung transplantation. Can J Anesth. 2003;50:707-11.
28. Della Rocca G, Costa MG, Coccia C, et al. Preload and haemodynamic assessment during liver transplantation: a comparison between the pulmonary artery catheter and transpulmonary indicator dilution techniques. Eur J Anaesthesiol. 2002;19:868-87.
29. Della Rocca G, Costa MG, Feltracco P, et al. Continuous right ventricular end diastolic volume and right ventricular ejection fraction during liver transplantation: a multi center study. Liver Transpl. 2008;14:327-332.
30. Della Rocca G, Costa MG, Pompei L, et al. Continuous and intermittent cardiac output measurement: pulmonary artery catheter versus aortic transpulmonary technique. Br J Anaesth. 2002;88:350-6.
31. Della Rocca G, Pompei L, Costa MG, et al. Fenoldopam mesylate and renal function in patients undergoing liver transplantation: a randomized, controlled pilot trial. Anesth Analg. 2004;99:1604-9.
32. De Wolf A. Hemodynamic monitoring during orthotopic liver transplantation. Transpl Proc. 1993;25:1863.
33. De Wolf AM, Aggarwal S. Monitoring preload during liver transplantation. Liver Transpl. 2008;14:268-9.
34. De Wolf AM, Begliomini B, Gasior TA, et al. Right ventricular function during orthotopic liver transplantation. Anesth Analg. 1993;76:562.
35. Diaz S, Perez-Pena J, Sanz J, et al. Haemodynamic monitoring and liver function evaluation by pulsion cold system Z-201 (PCS) during orthotopic liver transplantation. Clin Transplan. 2003;17:47.
36. Donovan CL, Marcovitz PA, Punch JD, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. Transplantation. 1996;61:1180-8.
37. Ducerf C, Mechet I, Landry JL, et al. Hemodynamic profiles during piggyback liver grafts using arterial or portal revascularization. J Am Coll Surg. 2000;190:89-93.
38. Dulitz MG, De Wolf AM, Wong H, et al. Compression of brachial plexus during right lobe liver donation as a cause of brachial plexus injury: a case report. Liver Transplant. 2005;11:233-5.
39. European Liver Transplant Registry 1998–2003. Available at: http://www.eltr.org.
40. Fernandez M, Mejias M, Angermayr B, et al. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal–systemic collateral vessels in portal hypertensive rats. J Hepatol. 2005;43: 98-103.
41. Findlay JY, Jankowski CJ, Vasdev GM, et al. Fast track anesthesia for liver transplantation reduces postoperative ventilation time but not intensive care unit stay. Liver Transpl. 2002;8:670-5.
42. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol. 2007;50:e159-242.

by mansdocs.com

43. Ganter MT, Hofer CF. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Int Anesth Res Soc. 2008;106(5):1366-75.
44. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362:823-32. [Erratum, N Engl J Med 2011;364:490.]
45. Garcia N Jr, Mihas AA. Hepatic hydrothorax. Pathophysiology, diagnosis, and management. J Clin Gastroenterol. 2004;38:52-8.
46. Gatt A, Riddell A, Calvaruso V, et al. Enhanced thrombin generation in patients with cirrhosis- induced coagulopathy. J Thromb Haemost. 2010;8:1994-2000.
47. Gelb AW, Robertson KM. Anaesthetic management of the brain dead for organ donation. Can J Anaesth. 1990;37: 806-12.
48. Greim CA, Roewer N, Thiel H, et al. Continuous cardiac output monitoring during adult liver transplantation: thermal filament technique versus bolus thermodilution. Anesth Analg. 1997;85:483-8.
49. Gwak MS, Kim JA, Kim GS, et al. Incidence of severe ventricular arrhythmias during pulmonary artery catheterization in liver allograft recipients. Liver Transpl. 2007;13:1451-4.
50. Hasse JM, Blue LS, Liepa GU, et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN. 1995;19:437-43.
51. Hasse JM. Nutrition in clinical practice. Gastrointestinal disorders and their connections to nutrition. Nutr Clin Pract. 2008;23:259.
52. Henriksen JH, Møller S. Cardiac and systemic haemodynamic complications of liver cirrhosis. Scandinavian Cardiovascular Journal. 2009;43(4):218-25.
53. Hsaiky L, Bajjoka I, Patel D, et al. Postoperative use of intense insulin therapy in liver transplant recipients. Am J Transplant. 2008;8 (S2):260.
54. Hudson J, Wurm W, O'Donnell T, et al. Ibuprofen pretreatment inhibits prostacyclin release during abdominal exploration in aortic surgery. Anesthesiology. 1990;72:443-9.
55. Hwang GS, McCluskey SA. Anesthesia and outcome after partial hepatectomy for adult-to-adult donor transplantation. Curr Opin Organ Transplant. 2010;15:377-82.
56. Kelly D, Jara P, Rodeck B, et al. Tacrolimus and steroids versus ciclosporin microemulsion, steroids, and azathioprine in children undergoing liver transplantation: randomised European multicentre trial. Lancet. 2004;364:1054-61.
57. Kelly D, Sibal A. Current status of liver transplantation. Indian J Pediatr. 2003;70:731-5.
58. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-26.
59. Krenn Claus-Georg, De Wolf Andre M. Current approach to intraoperative monitoring in liver transplantation. Curr Opin Organ Transpl. 2008;13:285-90.
60. Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl. 2000;6:443-50.
61. Krowka MJ, Porayko MK, Plevak DJ, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. Mayo Clin Proc. 1997;72:44-53.
62. Krowka MJ, Swanson KL, Frantz RP, et al. Portopulmonary hypertension: results from a 10-year screening algorithm. Hepatology. 2006;44:1502-10.
63. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med. 2004;32:691.
64. Lisman T, Bakhtiari K, Pereboom IT, et al. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. J Hepatol. 2010;52:355-61.
65. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. Liver Transpl. 2005;11:973-9.
66. Mandell M, Hang Y. Pro: early extubation after liver transplantation. J Cardiothorac Vasc Anesth. 2007;21:752-5.
67. Mandell M, Lezotte D, Kam I, et al. Reduced use of intensive care after liver transplantation: influence of early extubation. Liver Transpl. 2002;8:676-81.
68. Mandell MS, Lockrem J, Kelley SD. Immediate tracheal extubation after liver transplantation: experience of two transplant centers. Anesth Analg. 1997;84:249-53.
69. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med. 1990;323:1781-88.
70. Marquez J, Martin D, Virji MA, et al. Cardiovascular depression secondary to ionic hypocalcemia during hepatic transplantation in humans. Anesthesiology. 1986;65:457-61.
71. Massicotte L, Beaulieu D, Thibeault L, et al. Coagulation defects do not predict blood product requirements during liver transplantation. Transplantation. 2008;85:956-62.
72. Massicotte L, Lenis S, Thibeault L, et al. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. Liver Transpl. 2006;12:117.
73. Massicotte L, Lenis S, Thibeaults L, et al. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantations. Liver Transplantation. 2006;12:117-23.
74. Mckeown DW, Bonser RS, Kellum JA. Management of the heart beating brain-dead organ donor. Br J Anaesth. 2012;108 Suppl 1:i96-i107.
75. Mechtcheriakov S, Graziadei IW, Mattedi M, et al. Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation. Liver Transpl. 2004;10:77-83.
76. Moghissi E, Korytkowski M, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association Consensus statement on inpatient glycemic control. Endocrine Pract. 2009;15:353-69.

by mansdocs.com

77. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57;268-78.
78. Montalto P, Vlachogiannakos J, Cox DJ, et al. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. J Hepatol. 2002;37:463-70.
79. Moreau R. The growing evidence that renal function should be improved in patients with cirrhosis and hepatorenal syndrome before liver transplantation. Editorial. J Hepatol. 2004;40:159-61.
80. Moreno C, Sabate A, Figueras J, et al. Hemodynamic profile and tissular oxygenation in orthotopic liver transplantation: influence of hepatic artery or portal vein revascularization of the graft. Liver Transpl. 2006;12:1607-14.
81. Moretti EW, Robertson KM, Tuttle-Newhall JE, et al. Orthotopic liver transplant patients require less postoperative morphine than do patients undergoing hepatic resection. J Clin Anesth. 2002;14(2):416-20.
82. Murray KF, Carithers RL. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology. 2005;41(6):1407-32.
83. Møller S, Henriksen JH. The systemic circulation in cirrhosis. In: Gines P, Arroyo V, Rodes J, Schrier RW, eds. Ascites and renal dysfunction in liver disease. Malden: Blackwell. 2005:139-55.
84. Niemann CU, Eilers H. Abdominal organ transplantation. Minerva Anesthesiol. 2010;76:266-75.
85. Ozier Y, Klinck JR. Anesthetic management of hepatic transplantation. Curr Opin Anesthesiol. 2008;21:391-400.
86. Ozier Y, Pessione F, Samain E, et al. French study group on blood transfusion in liver transplantation. Institutional variability in transfusion practice for liver transplantation. Anesth Analg. 2003;97:671.
87. O'Grady JG, Burroughs A, Hardy P, et al. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. Lancet. 2002;360:1119-25.
88. O'Leary JG, Davis GL. Conivaptan increases serum sodium in hyponatremic patients with end-stage liver disease. Liver Transpl. 2009;15:1325-9.
89. Park C, Hsu C, Neelakanta G, et al. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. Transplantation. 2009;87:1031-6.
90. Plauth M, Cabré E, Riggio O, et al. ESPEN Guidelines on Enteral Nutrition: Liver Disease. Clinical Nutrition. 2006;25:285-94.
91. Plotkin JS, Benitez RM, Kuo PC, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. Liver Transpl Surg. 1998;4:253-7.
92. Plotkin JS, Kuo PC, Rubin LJ, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. Transplantation. 1998;65:457-9.
93. Plotkin JS, Scott VL, Pinna A, et al. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. Liver Transpl Surg. 1996;2:426-30.
94. Prentis JM, Manas DMD, Trenell MI, et al. Submaximal Cardiopulmonary Exercise Testing Predicts 90-Day Survival After Liver Transplantation. Liver transpl. 2012;18:152-8.
95. Ramsay MA, Simpson BR, Nguyen AT, et al. Severe pulmonary hypertension in liver transplant candidates. Liver Transpl Surg. 1997;3:494-500.
96. Ramsay MA, Spikes C, East CA, et al. The perioperative management of portopulmonary hypertension with nitric oxide and epoprostenol. Anesthesiology. 1999;90:299-301.
97. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on post transplantation outcome. A case control study. J Hepatol. 2004;40:140-6.
98. Roullet S, Pillot J, Freyburger G, et al. Rotation thromboelastometry detects thrombocytopenia and hypofibrinogenaemia during orthotopic liver transplantation. Br J Anaesth. 2010;104:422-8.
99. Ruiz-del-Arbol L, Urman J, Fernandez J, et al. Circulatory function and hepatorenal syndrome in cirrhosis. Hepatology. 2005;42:439-47.
100. Salooja N, Perry DJ. Thromboelastography. Blood Coag Fibrin. 2001;12:327-37.
101. Sanchez AJ, Aranda-Michel J. Nutrition for the liver transplant patient. Liver Transpl. 2006;12:1310-6.
102. Sanchez AJ, Aranda MJ. Nutrition in hepatic failure and liver transplantation. Rev Gastroenterol Mex. 2007;72:365-70.
103. Santamaria F, Sarnelli P, Celentano L, et al. Noninvasive investigation of hepatopulmonary syndrome in children and adolescents with chronic cholestasis. Pediatr Pulmonol. 2002;33:374-9.
104. Schroeder RA, Collins BH, Tuttle-Newhall E, et al. Intraoperative fluid management during orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 2004;18:438-41.
105. Schumann R. Intraoperative resource utilization in anesthesia for liver transplantation in the United States: a survey. Anesth Analg. 2003;97:21-8.
106. Siniscalchi A, Begliomini B, De Pietri L, et al. Increased prothrombin time and platelet counts in living donor right hepatectomy: implications for epidural anesthesia. Liver Transpl. 2004;10:1144-9.
107. Smyrniotis V, Kostopanagiotou G, Theodoraki K, et al. The role of central venous pressure and type of vascular control in blood loss during major liver resections. Am J Surg. 2004;187:398.
108. Spier BJ, Larue SJ, Teelin TC, et al. Review of complications in a series of patients with known gastro-esophageal varices undergoing transesophageal echocardiography. J Am Soc Echocardiogr. 2009;22:401-3.
109. Starkel P, Vera A, Gunson B, et al. Outcome of liver transplantation for patients with pulmonary hypertension. Liver Transpl. 2002;8:382-8.
110. Steadman R. Con: immediate extubation for liver transplantation. J Cardiothorac Vasc Anesth. 2007;21:756-7
111. Steadman RH. Anesthesia for liver transplant surgery. Anesthesiol Clin N Am. 2004;22:687-711.
112. Swygert TH, Roberts LC, Valek TR, et al. Effect of intraoperative low-dose dopamine on renal function in liver transplant recipients. Anesthesiology. 1991;75:571-6.

by mansdocs.com

113. Tiukinhoy-Laing SD, Rossi JS, Bayram M, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol. 2006;98:178-81.
114. Tripodi A, Mannucci PM. Abnormalities of hemostasis in chronic liver disease: Reappraisal of their clinical significance and need for clinical and laboratory research. J Hepatol. 2007;46:727.
115. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology. 2005;41:553-8.
116. Tripodi A. Hemostasis abnormalities in chronic liver failure. In: Gines P, Kamath PS, Arroyo V (Eds). Chronic Liver Failure: Mechanisms and Management. New York: Springer; 2010. pp. 289-303.
117. Umgelter A, Reindl W, Wagner KS, et al. Effects of plasma expansion with albumin and paracentesis on haemodynamics and kidney function in critically ill cirrhotic patients with tense ascites and hepatorenal syndrome: a prospective uncontrolled trial. Critical Care. 2008;12:R4.
118. Umphrey LG, Hurst RT, Eleid MF, et al. Preoperative dobutamine stress echocardiographic findings and subsequent short-term adverse cardiac events after orthotopic liver transplantation. Liver Transpl. 2008;14:886-92.
119. Walsh TS, Garden OJ, Lee A. Metabolic, cardiovascular, and acid-base status after hepatic artery or portal vein reperfusion during orthotopic liver transplantation. Liver Transpl. 2002;8:537-44.
120. Wang WD, Liang LJ, Huang XQ, et al. Low central venous pressure reduces blood loss in hepatectomy. World J Gastroenterol. 2006;12:935.
121. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. JAMA. 2007;298:423-9.
122. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology. 2002;35:478-91.
123. Williams K, Lewis JF, Davis G, et al. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. Transplantation. 2000;69:2354-6.
124. Xia VW, Steadman RH. Antifibrinolytics in orthotopic liver transplantation. Liver Transpl. 2005;11:10-18.
125. Yun BC, Kim WR, Benson JT, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology. 2009;49:1610-5.

by mansdocs.com

CHAPTER

29

Critical Care Aspects in Adult Liver Transplantation

Shrikanth Srinivasan, Deepak Govil

INTRODUCTION

Liver transplantation is a treatment option for both acute liver failure (ALF) and end-stage liver disease (ESLD). ALF is by far more morbid of the two states with acute and near-catastrophic multiorgan failure with the liver as the central and precipitating failed organ. Cirrhosis, on the other hand, is a slow and insidious liver dysfunction resulting in gradual failure of all other systems in the body. As a consequence of these scenarios, all the organ dysfunctions and failures are carried through the phase of transplant surgery and the post-transplant intensive care phase.

Advances in pretransplant treatment of cirrhosis-related organ dysfunction, intraoperative patient management, and improvements in the treatment of rejection and infections have made human liver transplantation an effective and valuable option for patients with ESLD.

In recent years, sicker patients with multiple comorbidities and organ dysfunction have been undergoing liver transplantation; appropriate critical care management is required to support prompt graft recovery and prevent systemic complications.

Early postoperative management is highly demanding as significant changes may occur in both the allograft and the "distant" organs. A functioning transplanted liver is usually associated with organ system recovery, resulting in a new life for the patient. Though it is the degree of functioning of the transplanted liver that largely determines the other system functions, their dysfunction may be an outcome of an independent entity, not least important among which is sepsis. In the unfortunate event of graft dysfunction, the unavoidable development of multiorgan failure will require an enhanced level of critical care support and a prolonged intensive care unit (ICU) stay.

Intensive care management of liver-transplanted patients mainly centers on rapid hemodynamic stabilization, correction of coagulopathy, early weaning from mechanical ventilation, proper fluid administration, kidney function preservation, graft rejection prevention, and infection prophylaxis.

FUNCTION OF THE LIVER ALLOGRAFT

A smooth ICU course after liver transplant is dependent on satisfactory graft function, which can be assessed by clinical parameters, such as wakefulness, normal mentation, improvement of muscle power, stable respiratory effort, change in drain fluid from serosanguinous to ascites, improvement in urine output, and lab parameters including improvement in acidemia, stable platelet counts, stable and improving INR without use of fresh-frozen plasma, improving serum lactate, declining transaminases, and normal flow patterns on Doppler.

Serum bilirubin concentration gradually falls to normal levels during the first week. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peak during the first 3 days and slowly level off, from then, in case of a healthy uptake of the grafted liver. Gamma-glutamyl transferase and alkaline phosphatase, which are canalicular enzymes, rise to 4–5 times of normal and then return to normal in the next few days. Synthetic functions normalize after the third day. While all of the above

by mansdocs.com

parameters may remain equivocal, the deteriorating clinical condition with multiorgan dysfunction may be the main clue to the nonfunction of transplanted liver. In such situations, liver biopsy (percutaneous or transjugular) may provide the ultimate answer.

Hyperacute graft rejection is very rare in liver transplantation and occurs due to the presence of preformed antibodies. On the other hand, acute cellular rejection is as common as 15–25%. It can be present from within few days to a few years and so in reality the term acute is inaccurate. Here, a rise in serum bilirubin is associated with rise in aminotransferases and canalicular enzymes. Clinical symptomatology can be rather nonspecific with loss of appetite, pruritus, and fever without tachycardia. This picture is associated with increased hepatic artery resistive index on Doppler. The diagnosis is made on liver biopsy and treatment based on severity or the degree of rejection (Banff score). The so-called "chronic" rejection can also occur at any time and is evidenced by cholestatic features clinically and advancing arteriopathy and degenerating bile ducts on liver histology, resulting in terminal liver failure eventually. Chronic rejection is extremely uncommon, accounting for less than 5% of all cases of graft loss, and may occur due to untreated acute rejection, noncompliance to immunosuppression medication, or some immunological mechanisms which are not very well understood.

Various kinds of anastomotic problems can be present in the early postoperative days with varying incidence. Hepatic artery thrombosis (HAT), with incidence of 4–12%, can present as sudden deterioration in hemodynamics, acute respiratory distress syndrome (ARDS), severe coagulopathy, sudden and marked elevation of aminotransferases, with commonly accompanying liver abscesses due to bile duct strictures. Complications involving the portal vein are seen in 1.7–6% of liver transplant recipients.

Persistent ascites, enteric congestion and bleeding denoting portal hypertension, and later variceal hemorrhage may point to portal vein thrombosis (PVT). Doppler ultrasound followed by a traditional angiogram or magnetic resonance angiogram (MRA) will be diagnostic. Appropriate surgical or radiological intervention can be both, graft and life saving in these conditions. Patency of biliary tract can be jeopardized, either due to direct insult to the duct system or because of feeder vessel obstruction. Biliary tract complications account for up to 15% of postoperative surgical complications. These are more common in partial grafts than in whole liver grafts. Again surgical interventions and/or radiological interventions are imperative.

Mediators from the liver or intestine may lead to a reperfusion syndrome after the graft is revascularized, which may manifest as hypotension from peripheral vasodilation, bradycardia, hyperkalemia, and pulmonary hypertension.

SYSTEMIC MANAGEMENT

Pulmonary System

The unique pathophysiology of patients with ESLD has important implications for their critical care treatment, particularly in the postoperative state. Typically, endotracheal intubation and mechanical ventilation are continued into the postoperative period. As a standard practice, all the modalities of monitoring and medication are continued into the postoperative period, the degree of which will be decided depending on the progress of the patient. In most low risk transplant with an uneventful intraoperative course, all anesthetic and relaxant medications can be discontinued and patient can be fast tracked to weaning and extubation. Otherwise, the patient continues to be infused with longer acting anesthetics, analgesics, and muscle relaxants. In such cases, the process of weaning and time of extubation will depend on the patient's subsequent progress which in turn is largely guided by "kick-starting" of the engrafted liver. Various clinical results suggest that an early or very early tracheal extubation (immediately in the operating room or within 3 hours postoperatively) has been associated with a persistent maintenance of satisfactory gas exchange. The incidence of reintubation was not increased thereafter when compared to patients extubated later.

The risk factors for delayed extubation are summarized in Box 1.

A difficult weaning from mechanical ventilation is very often a consequence of postoperative respiratory complications, which can be attributed to massive transfusion, pleural effusion, inadequate clearance of bronchial secretions, pneumonia and adverse effects of immunosuppressive therapy. ARDS is one of the prominent complications following orthotopic liver transplantation (OLTx).

Its main causes include a severe reperfusion syndrome, substantial blood loss, prolonged operation and early postoperative infections. The management and treatment of respiratory complications, including ARDS, are primarily supportive, with obligatory mechanical assistance in cases

by mansdocs.com

Box 1: Risk factors for delayed extubation in liver transplant patients.

- Severity of liver disease before surgery (Child-Pugh score)
- UNOS status
- Age
- Duration of graft ischemia
- Intraoperative blood requirements
- Body temperature on ICU admission
- Renal dysfunction
- Hepatic encephalopathy
- Need for inotropes or vasopressors
- Inadequate oxygenation

Source: Adapted from Biancofiore et al.
(UNOS: United Network for Organ Sharing; ICU: Intensive care unit).

of ventilatory failure. If postoperative respiratory failure is severe enough to require a prolonging of mechanical ventilation, ventilatory strategies that minimize insults to both the lung and the allograft should be used. Airway pressures and positive end-expiratory pressure (PEEP) should be set in order to improve oxygenation without simultaneously impairing liver outflow.

In liver recipients affected by severe ARDS, low tidal volume (6 mL/kg of ideal body weight), relatively high respiratory rates and PEEP confer a survival advantage by keeping the lung open and avoiding atelectasis and shear stresses on lung units. Mechanical ventilation with high PEEP has been reported to impair liver outflow. Besides determining an increased retrograde blood accumulation and liver edema, an excessive PEEP (>10 cm H_2O) may also depress the splanchnic perfusion and hepatic performance by increasing venous stasis in the portacaval system and depressing cardiac output .

In case of a suspected infection, bronchoalveolar lavage has to be obtained for quantitative bacteriological and fungal cultures, which should be followed by sensitive antibiotics or antifungal agents. Early application of noninvasive ventilation rather than just supplemental oxygen can reduce the incidence of reintubations, major or fatal complications and overall mortality.

Preventing reintubation should be a major aim of management of respiratory failure in these immunocompromised patients.

Good pain control, chest physiotherapy, and incentive spirometry with functioning graft will improve this scenario. Widespread vasodilatation with vascular shunting in liver disease will have its reflection on the pulmonary system. In a more etiopathogenic sense, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH) may continue into the post-transplant period. Introduction of pulmonary artery catheter is essential for management of these patients. The HPS is hypoxemia in the background of liver disease with air contrast echocardiogram (Bubble study) demonstrable intrapulmonary shunting. This syndrome presents with dyspnea and desaturation on erect posture, platypnea and orthodeoxia. Their ventilation-perfusion mismatch resolves after a few days of successful transplantation. Fixed nonreversible shunt denotes poor prognosis. Pulmonary hypertension is more likely in cirrhotic patients with worsening portopulmonary shunting. This can affect right ventricular function and may have to be corrected with epoprostenol (prostacyclin-PG_{12}), which is a potent pulmonary and systemic vasodilator. Severe PPH is a contraindication transplantation. Pulmonary hypertension developing first time after transplant is usually due to pulmonary embolism.

Cardiovascular System

Besides relying on intrinsic hepatic cell recovery, maintenance of postoperative graft function also depends on optimization of liver hemodynamics and prevention of venous stasis. Subclinical hypovolemia, or excessive cardiac filling resulting in pulmonary edema and deterioration of gas exchange, may lead to inadequate graft perfusion and increase postoperative morbidity. Patients with cirrhosis tend to have impaired ventricular contractility in response to physiologic stress or pharmacologic stimulation.

Additionally, metabolic disturbances, in the form of acidosis, hypothermia, and electrolyte disturbance can further reduce cardiac performance and lead to circulatory instability. Hemodynamic depression may also be a long-term result of the reperfusion syndrome and/or a consequence of hypocalcemia-induced citrate intoxication from massive transfusion. Other causes of postoperative hypotension are a preexisting dilated cardiomyopathy, the potential for coronary artery disease, and an unrecognized hypovolemia from various factors, including hemorrhage, third space losses, and ongoing ascites formation. Sepsis may further complicate the picture. Elevated venous pressures will lead to hepatic congestion, and this may in turn increase the portal pressure. As a result of this, graft function may further suffer and lead to bacterial translocation

by mansdocs.com

and endotoxemia. To avoid such sequences of events, hypotension has to be classified as cardiac or vasodilatory. Moderate filling followed by vasoconstriction should treat this. Whereas, inotropic support can be provided by dobutamine and adrenaline, vasoconstriction can be achieved with low dose noradrenaline or vasopressin. Cardiac tamponade has to be excluded in face of low cardiac output and high filling pressures.

Systemic hypertension is common in the early postoperative period in a patient with a well functioning graft. It generally occurs either due to lack of analgesia or sedation in this setting. Later in the course of patient recovery, hypertension occurs due to cyclosporine or tacrolimus. Treatment is usually initiated when the systolic blood pressure is greater than 160 mm Hg or the diastolic blood pressure greater than 100 mm Hg. Atrial fibrillation may occur due to perioperative fluid shifts, acid base imbalance and electrolyte abnormalities. Treatment includes etiological management, beta-blockers and calcium antagonists, but amiodarone should be avoided if possible because of its potential hepatotoxicity.

Unrecognized coronary artery disease is associated with a mortality of up to 50% and morbidity of 80%. The possibility of perioperative myocardial infarction causing left ventricular dysfunction must be kept in mind in cases of refractory circulatory dysfunction. Preoperative dobutamine stress echocardiogram (DSE) is a good screening test for occult coronary artery disease because it assesses the adequacy of myocardial oxygen supply. In addition, assessment must be made of valvular function and the presence of intrapulmonary shunting (by contrast echocardiogram) and PPH. A negative DSE predicts a good prognosis, that is, a low probability of perioperative cardiac events.

While high cardiac output is common in cirrhosis, a relative low cardiac output status may be seen in cirrhotic patients with cardiomyopathy and amyloidosis. Some patients, especially those with alcohol-related cirrhosis, may present with reversible dilated cardiomyopathy (takotsubo cardiomyopathy) after liver transplantation. These patients will need advanced hemodynamic monitoring such as Swan-Ganz or pulse contour analysis computer (PiCCO) and inotropic support, supportive care and possibly intra-aortic balloon counterpulsation (IABP) support.

Postoperative "subclinical" pulmonary edema is not infrequent with at least 50% of these episodes developing within the first 24 hours. The rapid improvement of systemic vasodilatation, which can result in a sudden increase in the afterload, is another potential cause of excessive strain on the heart. Because of potential cardiocirculatory instability and the need to optimize cardiac output and organ perfusion, hemodynamic monitoring must be strictly carried out in the immediate postoperative period.

Fluid and Electrolytes

Intraoperative hypovolemia and significant blood loss usually require massive amounts of intravenous fluid and blood products to preserve cardiac output and organ perfusion. However, massive blood transfusion with fluid administration is not free from complications in the postoperative period. One of the significant predictors of readmission to the ICU is the amount of blood product administered intraoperatively.

Generous fluid replacement may result in volume overload, water-sodium retention, a capillary leak syndrome in the third space, and may further aggravate graft congestion and edema caused by ischemia-reperfusion syndrome.

Once postoperative hemodynamics have been stabilized, an appropriate negative fluid balance on the first day after operation apparently decreases the incidence of early pulmonary complications and may be associated with improved oxygen delivery to the graft. Lowering right ventricular volume and pressure would create a venous pressure gradient between the portal and central venous circulation that draws blood through the donor graft.

A rational approach to maintain circulating volume is by providing two-thirds of required fluids with crystalloid and replacing half of drain losses with 5% albumin. The recipient is generally kept in an euvolemic or slightly hypovolemic state in the post-transplant period, with minimal intravenous infusions, to optimize graft function and avoid pulmonary edema. If needed, 5% dextrose with 0.45% normal saline (NS) is used unless the serum sodium is less than 130 mEq/L, when 5% dextrose with 0.9% NS can be used. Gelatins are generally preferred to starches in these patients given the current literature which shows increased incidence of renal dysfunction with starches. Packed red cell and albumin transfusions are preferred when volume expansion is required.

Electrolyte imbalance is quite common in these patients. Hyponatremia should be gradually corrected with judicious use of fluids with a target serum sodium rise of less than 10–12 mEq/dL/day is desirable. Hypomagnesemia is common in cirrhotic patients and may be exacerbated in the post-transplant patient by excessive blood

by mansdocs.com

loss and medications [calcineurin inhibitors (CNIs), loop diuretics and amphotericin B]. Recovering graft has a high requirement for phosphate and magnesium and these should be replaced adequately. Ionized serum calcium levels should be monitored as total calcium levels depend on the albumin concentration which may fluctuate widely in the early post-transplant period. Pretransplant hypocalcemia due to malnutrition and vitamin D dysfunction may be exacerbated early in the post-transplant patient by citrate chelation (with blood transfusion), gastrointestinal malabsorption and hepatocyte injury resulting in an intracellular shift of calcium. Hypercalcemia and hypermagnesemia are rare.

Renal System

Pretransplant renal dysfunction is an independent predictor of post-transplant morbidity and mortality. Up to 25% of recipients suffer from renal impairment prior to transplantation, and nearly two-thirds of transplant recipients show impaired post-transplant renal function. It has been found that in the post-transplant period there is a 40% decline in the glomerular filtration rate at the end of 6 weeks after which it stabilizes.

The etiological reasons for renal dysfunction in the post-transplant phase include pretransplant renal dysfunction, which may be due to either acute tubular necrosis (ATN) or hepatorenal syndrome or other medical problems, tubular damage due to peritransplant hypotension, graft dysfunction, ATN from postoperative sepsis and drug-induced injury (cyclosporine, tacrolimus, amphotericin, aminoglycosides, etc.). Management of renal dysfunction depends on the etiology. Those with Hepatorenal syndrome (HRS) are more likely to require renal replacement therapy (RRT) with about 10% progressing to develop ESRD (end-stage renal disease) (end-stage renal disease). Intraoperative management of hypotension, use of venovenous bypass and avoidance of nephrotoxic drugs are important renoprotective strategies. Nephrotoxicity is a known complication of CNIs used to prevent rejection.

Reducing the dosage, use of CNI sparing antirejection protocol or delaying introduction of CNIs in those with high probability of renal dysfunction and use of calcium channel blockers in CNI related hypertension have been found to be useful strategies in long-term renal protection. Oliguria may be the earliest warning sign of renal dysfunction. Eight to ten percent of transplant recipients require RRT in the immediate postoperative period. Dialysis, preferably lactate free continuous renal replacement therapy (CRRT) is required to stabilize these patients. So-called renoprotective agents like dopamine, calcium channel blockers or prostaglandins have not been proven to be of value. Combined liver and kidney transplant is an option reserved for those patients with pretransplant renal dysfunction due to other concomitant medical illness or intrinsic renal disease.

Gastrointestinal System

Many patients are severely malnourished before transplantation. As most patients have brisk return of gastrointestinal function, early enteral nutrition is the goal, except in patients with Roux-en-Y choledochojejunostomy. Upper gastrointestinal bleed is usually due to gastritis or stress ulceration. In case of a Roux-en-Y being performed, the Roux loop could be a source of bleed. In general with good graft function, upper gastrointestinal bleeding is rare. PVT may result in recurrence of varices and bleeding. Post-transplant pancreatitis is a feared complication of liver transplantation. Conservative management is usually preferred to aggressive measures.

Central Nervous System

Careful evaluation of a patient's mental status should be constantly performed during the ICU stay as neurological complications are common after OLTx. Clinical series have documented neurological disorders in 8.3–47% of all patients receiving liver transplantation. Rapid recovery from encephalopathy is expected in the presence of good graft.

The most frequent complications are encephalopathy, brain hemorrhage, and seizure. Patients with neurologic symptoms prior to transplantation are at greater risk for postoperative neurologic disturbances. A poor graft function may result in recurrence of encephalopathy. The etiology of encephalopathy is often difficult to determine as multiple factors such as subarachnoid hemorrhage, meningitis, infarction, spinal cord necrosis and cytomegalovirus infection may be involved. Acute change in mental status and occurrence of seizures should need checking up of drug, electrolytes and blood glucose levels. Focal deficit should lead to suspicion of stroke or embolism.

Seizures are the second most common neurological complications reported in liver transplanted patients. Seizure may be a consequence of factors including stroke, metabolic disturbances, electrolyte disorders, drug toxicity (antibiotics, CNI), previous history of epileptic seizures.

by mansdocs.com

Psychosis is another feared complication in transplant recipients. It has a multifactorial etiology and could be due to prolonged ICU stay, use of steroids and other immunosuppressants. The fact that most antipsychotics are hepatotoxic is a major impediment in the treatment of this condition. Psychosis resulting in a noncompliant patient, can be a major stumbling block in rapid recovery, due to ineffective delivery of medication, physiotherapy and mobilization.

Endocrine and Metabolic Problems

Hyperglycemia is common because of surgical stress, steroid administration and insulin resistance associated with liver failure and there is increasing evidence to deploy tight control regimens. Hypoglycemia may be a sign of inadequate graft function or severe sepsis.

Hypothermia is common in the post-transplant patient and can precipitate metabolic acidosis and accentuate coagulopathy. Mild metabolic acidosis is common in the first few hours after transplantation. Optimum fluid and inotropic management should attenuate this acidosis. Persistent metabolic acidosis in the absence of other causes should warrant suspicion of graft dysfunction. Slightly delayed acidosis may indicate sepsis. Serial lactate levels are helpful in managing such situations.

Adrenal insufficiency and hypothyroidism are sometimes seen in these patients and have to be corrected after establishing the diagnosis.

Coagulopathy

Coagulopathy results from pre-existing portal hypertension, inadequate clotting factor synthesis, hypersplenism, fibrinolysis, hypocalcemia and dilution. The risk of bleeding must be balanced against the risk of HAT or PVT, so over correction should be avoided. Hence, monitoring of coagulation becomes mandatory after liver transplantation. Thrombocytopenia usually regresses within 2 weeks, but in some individuals it lasts longer due to persistent splenomegaly.

Thromboelastography (TEG), a method for evaluating the viscoelastic properties of the blood clot, can be used to complement the standard coagulation parameters in these patients. The TEG can be useful in differentiating between bleeding secondary to incomplete surgical hemostasis, platelet dysfunction and anomalies in coagulation factors and therefore, can help in optimizing and minimizing blood component usage by guiding use of selective blood component therapy. The TEG guided replacement can reduce transfusions and attendant complications. It may also be useful in detecting a hypercoagulable state, not reflected by standard coagulation parameters, which may be present after any major surgery and thus, may guide antithrombotic therapy with increased safety. The TEG has further advantages of allowing rapid bedside monitoring and may be useful in assessing the graft function.

Platelet dysfunction due to renal insufficiency can be managed with desmopressin. Replacement of blood products is necessitated in the presence of active bleeding or any planned intervention. Otherwise, maintenance of an INR between 1.5 and 2, a platelet count greater than 50×10^9/L and a fibrinogen level greater than 100 mg/dL is satisfactory.

Infection

Infections remain problematic following OLTx, and are still the primary causes of death. Prolonged hospital stay before the transplant and the immunocompromised status predispose the recipient to colonization with resistant microorganisms. Due to heavy immunosuppression, the early postoperative period poses greater risks of infection. Bacterial and fungal infections are common in the early post-transplant period; viral infections are seen much later in this population.

The source of the infecting organisms can be: (a) the donor organ and transfused blood products, (b) the reactivation of previous infection, (c) invasion by exogenous microorganisms or by endogenous flora. Wound infections, pneumonia, peritonitis, cholangitis, urinary and catheter-related infections, *Clostridium difficile* colitis, and liver abscesses are similar to the hospital-acquired infections observed in other surgical patients. Treatment of bacterial infections generally involves characterization of the infective agent (e.g. cultures and antibiotic sensitivities), source control (e.g. catheter removal and debridement) and antibiotic regimens based on the hospital antimicrobial susceptibility patterns. Immunosuppression must be reduced or even halted temporarily. Prophylactic postoperative antibiotics are primarily tailored to Gram-negative and Gram-positive organisms.

Prolonged surgery, multiple transfusions, malnutrition, hyperglycemia, requirement of dialysis and retransplantation are risk factors for fungal infections.

Common infections in post-transplant period are summarized in Table 1.

by mansdocs.com

Table 1: Common infections in postoperative period.

Early postoperative period (<30 days)	*Late postoperative period (>30 days)*
Bacteria:	
• Nosocomial infections (coagulase-negative, *Staphylococcus aureus*, *Gram-negative organisms: Enterobacter*, *Pseudomonas*)	• *Salmonella* • *Streptococcus pneumoniae* • *Hemophilus influenzae*
• *Clostridium difficile*	• *Nocardia*
• *Legionella*	• *Listeria*
Fungus:	
• *Candida*	• *Aspergillus*
• *Aspergillus*	• *Cryptococcus* • Reactivation of endemic mycoses (histoplasmosis and coccidioidomycosis)
Viral:	
• Reactivation of hepatitis B and C	• *Cytomegalovirus*
• Reactivation of herpes simplex virus	• Epstein-Barr virus • Reactivation of hepatitis B and C • Adenovirus • Varicella-zoster virus
Others	
	• Tuberculosis • *Pneumocystis carinii Pneumonia*

Immunosuppressive Therapy

Triple therapy is generally given in most centers based on a CNI, like tacrolimus or cyclosporine, in conjunction with an antiproliferative agent (mycophenolate mofetil) and a steroid. A dual regimen of steroids and a CNI has shown to be equally efficacious as triple therapy. The advantage of early use of triple therapy is that it may allow delaying the initiation of the CNI, while the post-transplant changes in renal function recover. One must maintain a balance between under-immunosuppression which may lead to graft rejection and over-immunosuppression which may lead to sepsis and malignancy.

Cyclosporine and tacrolimus seem to be similar in terms of graft and patients survival. However, tacrolimus is associated with fewer episodes of rejection and less need for steroid use. Tacrolimus is equally nephrotoxic and is associated with increased rates of diabetes and neurotoxicity but has a lower incidence of hypertension and hyperlipidemia.

POORLY FUNCTIONING ORGAN GRAFTS

Signs of early graft dysfunction can be considered with respect to: (a) hepatocellular dysfunction (biochemical, metabolic and synthetic), (b) extrahepatic organ dysfunction (neurological, metabolic, cardiovascular and renal impairment) and (c) sequel of portal hypertension. Unless dramatic presentations such as coma and shock occur, the signs and symptoms of poorly functioning allografts can be insidious and difficult to ascribe to graft malfunction.

Primary Graft Failure

Primary graft failure is characterized by the incapacity of the new graft to maintain the recipient metabolic homeostasis and is associated with a high risk of death without an emergency retransplantation. The incidence of primary failure ranges between 2% and 14%. Predisposing conditions such as donors' advanced age, hemodynamic instability, prolonged ischemia time, severe reperfusion damage, in many cases the exact causes are undetermined.

The patient exhibits signs of severe graft dysfunction including significant CNS changes, coma, serious coagulopathy, oliguria, jaundice and hypoglycemia. Liver transaminases are often greater than 5,000 U/L, factor less than 10% and prothrombin time greater than 20%. Treatment includes avoiding the administration of potassium, transfusing fresh frozen plasma every 4–6 hours or as needed and keeping the gastric pH greater than 5.0. A continuous 10% dextrose solution infusion may be needed to control hypoglycemia. Other suportive therapy utilizing prostaglandin E1, N-acetylcysteine, plasmapheresis and liver assisting devices have been described but with no confirmed positive results on a large scale. If no recovery of graft function occurs within 24–36 hours, relisting for retransplantation must be considered in order to avoid the development of multiorgan failure, in which case the mortality rate associated with retransplantation is very high.

Small-for-size Syndrome

Small-for-size syndrome has often been described in patients receiving a split liver or a partial liver graft from a live donor. Clinical presentation includes delayed synthetic function, poor bile production, cholestasis, and susceptibility to other complications including sepsis. It is believed that portal hypertension and congestion in a

by mansdocs.com

small graft are the cause of this syndrome. Supportive care and avoidance of infectious complications are critical for graft recovery and patient survival.

Vascular Thrombosis

Hepatic artery thrombosis (HAT) is a potentially life-threatening complication that is more common in children and in grafts where there is a size discrepancy between the donor artery and the native vessel (1.5–25%). Causes of HAT include poor arterial flow, increased sinusoidal resistance, preservation injury, stenosis of anastomosis and hypercoagulability. The HAT at an early stage typically leads to ischemic necrosis of the graft, sudden deterioration in hemodynamics, severe coagulopathy, and marked elevation of aminotransferases. Doppler ultrasound is the method for evaluating hepatic artery patency and arteriography is indicated when the vessel cannot be well identified. Arterial thrombectomy can be performed either by interventional radiology or surgical exploration. When revascularization fails, urgent retransplantation is mandatory.

Portal vein thrombosis is less common and mainly occurs as a result of pretransplant PVT or technical problems. Clinical manifestations include persistent ascites, enteric congestion and bleeding. Doppler ultrasound followed by a traditional angiogram or MRA is usually diagnostic. Surgical thrombectomy or radiological intervention is required to save the graft and avoid life-threatening complications.

Biliary Complications

Biliary complications have been described as the "Achilles heel" of liver transplantation. Biliary leaks are a common consequence of necrosis at the surgical anastomosis, technical errors or biliary tract ischemia. Lack of bile outflow through drainage, an increase of cholestatic enzymes and leukocytosis are indicative of a biliary complication. Ultrasound and/or abdominal CT scans may show ductal dilation or bile collection. The leak may resolve itself conservatively or may require treatment. Treatment options include endoscopic-retrograde pancreatography with biliary stenting or percutaneous transhepatic cholangiography with external drainage, or surgical repair. Biliary obstruction can be caused by ischemia, technical problems, and small duct size from partial allografts. Biliary strictures are usually treated with endoscopic or percutaneous balloon dilatation, stenting, or surgical re-exploration.

Nutritional Support

Factors, such as preoperative malnutrition, stress from surgery, and immunosuppressive therapy, enhance the need for nutritional support after transplantation. In the immediate postoperative period, protein catabolism is markedly increased, and hence, these patients should receive 1.5–2.0 grams of protein per kilogram of dry weight during this phase. Energy requirements are not significantly elevated; especially in an uncomplicated, nonseptic patient; therefore, calories should be provided at approximately 120–130% of the calculated basal energy expenditure (BEE). Patients should be encouraged to start oral diets as soon as tolerated.

CONCLUSION

Orthotopic liver transplantation has become an effective and valuable option for patients with ESLD. The principles guiding critical care for liver transplant patients, are to provide favorable circumstances for the new liver to start functioning and maintain the function of other organs to aid in this process. However, the ICU morbidity associated with some unpredictable factors, such as a difficult intraoperative course, delayed postoperative hemodynamic recovery, "marginality" of the implanted graft and "distant" organ dysfunction, is still substantial. Through prevention, recognition and prompt treatment of life-threatening events, liver transplant recipients may experience fewer postoperative complications, shorter length of ICU stay, and a better overall outcome.

BIBLIOGRAPHY

1. Feltracco P, Barbieri S, Galligioni H, et al. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3(3):61-71.
2. Gopal PB, Kapoor D, Raya R, et al. Critical care issues in adult liver transplantation. Indian J Crit Care Med. 2009; 13(3):113-9.
3. Razonable RR, Findlay JY, Riordan AO. Critical care issues after liver transplantation. Liver Transpl. 2011;17(5): 511-27.

by mansdocs.com

SECTION 5

Renal Care

by mansdocs.com

by mansdocs.com

CHAPTER

30

Diagnosis of Acute Kidney Injury

Vinay Malhotra

INTRODUCTION

Acute kidney injury (AKI) is asymptomatic until extremes of loss of function are reached and has no characteristic clinical findings. Diagnosis typically occurs in the context of another acute illness by laboratory tests. Patients with severe cases, however, may be symptomatic and present with listlessness, confusion, fatigue, anorexia, nausea, vomiting, weight gain, or edema. Patients can also present with oliguria (urine output less than 400 mL per day), anuria (urine output less than 50 mL per day), or normal volumes of urine (nonoliguric AKI). Other presentations of AKI may include development of uremic encephalopathy (manifested by a decline in mental status, asterixis, or other neurologic symptoms), anemia, or bleeding caused by uremic platelet dysfunction.

When a patient presents with raised serum creatinine, it is important to establish whether the patient has acute kidney injury (AKI) or chronic kidney disease (CKD) or a bout of acute illness superimposed on CKD. Abnormal serum creatinine before presentation; relevant risk factors (e.g. hypertension or diabetes); a slow clinical course for presenting illness; high serum concentrations of creatinine or phosphate, or both; and normocytic anemia all suggest the presence of chronic kidney disease. Renal ultrasonography might show small kidneys and provide evidence of chronic disease. Table 1 lists the differences between acute and chronic kidney disease based on history and investigations.

A careful and detailed patient history and physical examination are crucial for determining the cause of AKI (Table 2). The history should identify use of nephrotoxic medications or systemic illnesses that might predispose to AKI. Nephrotoxic drugs account for some part of AKI in 20–30% of patients. Physical examination should assess intravascular volume status and any skin rashes indicative of systemic illness.

Table 1: Acute versus chronic kidney disease.

	Acute kidney injury	*Chronic kidney disease*
• History of kidney disease, hypertension, abnormal urinalysis	-	+
• Small kidney size	-	+
• Return of renal function to normal with time	+	-
• Low carbamylated hemoglobin	+	-
• Hyperkalemia, acidemia, hyperphosphatemia,* anemia*	+	+

*More common in chronic kidney disease.

LABORATORY ASSESSMENT OF RENAL FUNCTION

The laboratory hallmarks of AKI are increased serum creatinine concentrations or raised plasma urea concentrations, or both. Unfortunately, these are insensitive markers of glomerular filtration rate (GFR) and are modified by nutrition, use of steroids, presence of

by mansdocs.com

Table 2: History and physical examination for categorizing acute kidney injury.

Type of acute kidney injury	*History findings*	*Physical examination findings*
• Prerenal	Volume loss (e.g. history of blood loss, vomiting, diarrhea, diuretic use, burns)	Tachycardia, hypotension, orthostatic hypotension, flat neck veins, poor skin turgor and dry oral mucosa.
	Cardiac disease Liver disease	Dilated neck veins, S3 heart sound, pulmonary rales, peripheral edema, congestive hepatomegaly, jaundice, ascites, caput medusa, palmar erythema, spider angiomas
• Intrinsic renal		
– Acute tubular necrosis	History of nephrotoxic medication exposure, hypotension, trauma or myalgias suggesting rhabdomyolysis, recent exposure to radiographic contrast agents	Muscle tenderness, compartment syndrome, assessment of volume status
– Glomerular	Systemic lupus erythematosus (SLE), systemic sclerosis, rash, arthritis, weight loss, fatigue, hepatitis C virus infection, HIV infection, red or cola colored urine, foamy urine, cough, sinusitis, hemoptysis	Edema, hypertension, rash, oral/nasal ulcers
– Interstitial	Medication use (e.g. antibiotic use, proton pump inhibitors), rash, arthralgia, fever	Fever, drug related rash
– Vascular	Nephrotic syndrome, trauma, flank pain, recent vascular intervention or surgery	Livedo reticularis, abnormal fundus exam, abdominal bruit
• Postrenal	Urinary urgency or hesitancy, hematuria, nocturia, stones, medication, cancer	Distended bladder, pelvis mass, prostate enlargement

Table 3: Biomarkers for acute kidney injury.

Biomarker types	*Biomarkers*
Functional markers	S Creatinine and plasma/serum cystatin C
Up-regulated proteins	Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) and Interleukin 8
Low-molecular weight proteins	Urine cystatin C
Enzymes	N-acetyl-β-D-glucosaminidase (NAG), Alpha-glutathione s-transferase (α-GST), Gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (AP)

gastrointestinal blood, muscle mass, age, sex, muscle injury and aggressive fluid resuscitation. Furthermore, they become abnormal only when GFR decreases by more than 50% and do not show dynamic changes in filtration rates. Despite these shortcomings, clinical monitoring remains based on the measurement of urea and creatinine concentrations. The above limitations of currently used kidney function markers have led to research to find more accurate kidney function biomarkers (serum and/or urine). Table 3 lists the biomarkers of AKI. However, prospective clinical trials are needed to establish their role in AKI to have them available for routine diagnostic testing in AKI.

In specific situations, other investigations are necessary to establish the diagnosis, such as measurement of creatine kinase and free myoglobin to identify possible rhabdomyolysis. Chest radiographs, blood films, measurement of nonspecific inflammatory markers, and assays that detect specific antibodies (e.g. those against glomerular basement membrane, neutrophil cytoplasm, DNA, or smooth muscle) are useful screening tests to help support the diagnosis of vasculitis, specific types of collagen disease or glomerulonephritis. If thrombotic thrombocytopenic purpura is suspected, concentrations of lactic dehydrogenase, haptoglobin, unconjugated bilirubin and free hemoglobin should also be measured. The presence of microangiopathic hemolysis in blood smears is also crucial for this diagnosis. In some patients, specific findings—e.g. cryoglobulins, Bence-Jones proteins—provide almost conclusive diagnosis.

Urinalysis also may provide useful clues to the diagnosis (Table 4). The presence of dysmorphic red blood cells and red blood cell casts is strongly suggestive of an acute

by mansdocs.com

Table 4: Diagnostic findings in acute kidney injury.

Condition	*Blood urea nitrogen/creatinine ratio*	*Urine sodium (mmol/L)*	*Fractional Excretion of sodium (%)*	*Urinalysis*	*Other findings*
• Prerenal acute kidney injury	> 20:1	< 20	< 1	Specific gravity > 1.015 Normal or hyaline casts	Fractional excretion of urea < 35%
• Intrinsic acute kidney injury					
– Acute tubular necrosis	10:1	> 40	> 3*	Specific gravity ~ 1.010 Muddy brown casts and tubular epithelial cells	Fractional excretion of urea < 60%
– Acute interstitial nephritis		> 20	> 1	Hematuria, white blood cells, white blood cell casts, eosinophiluria	Eosinophilia
– Acute glomerulonephritis		< 20	< 1	Dysmorphic red blood cells and red blood cell casts	Serum serologic studies
– Intratubular obstruction		Variable	Variable	Crystalluria** or non-albumin proteinuria (Bence-Jones proteinuria)	Monoclonal paraprotein on electrophoresis
– Acute vascular syndromes		< 20	Variable	Hematuria	Elevated lactate dehydrogenase with renal infarction
• Postrenal acute kidney injury	> 20:1	> 20	Variable	Variable	

* Fractional excretion of sodium can be low in radiocontrast nephropathy and pigment nephropathy.

**Calcium oxalate crystals with ethylene glycol ingestion; uric acid crystals in tumor lysis syndrome; drug crystals with acyclovir and indinavir toxicity.

Box 1: Indications for renal biopsy in acute kidney injury.

- Gradual onset of acute renal failure
- No obvious cause of acute renal failure
- Heavy proteinuria
- Significant hematuria (active urinary sediment)
- Clinical evidence or history of systemic disease
- Prolonged oliguria/anuria

glomerular process. The presence of white blood cells, white blood cell casts, and eosinophiluria suggests the diagnosis of acute interstitial nephritis (AIN). Tubular epithelial cells and muddy brown granular casts suggest the diagnosis of AIN. Heavy oxalate or uric acid crystalluria or the presence of drug crystals suggests intratubular crystal deposition, and the presence of non-albumin proteinuria suggests a diagnosis of myeloma kidney. Rarely, clinical signs, laboratory investigations, and radiological investigations are not sufficient to make a causative diagnosis with certainty. In such patients a renal biopsy might be necessary (Box 1).

RADIOLOGIC STUDIES

A number of radiologic studies are used to evaluate the patient with kidney disease. These tests are performed alone or in combination for the detection, diagnosis, and/or evaluation of multiple conditions. They are principally required to assess urinary tract obstruction, kidney stones, renal cyst or mass, disorders with characteristic radiographic findings, renal vascular diseases, and, in children and young adults, vesicoureteral reflux.

Because of safety, ease of use, and the information provided, the most commonly used radiographic technique in patients presenting with kidney disease is renal ultrasonography. Since obstruction is a readily reversible disorder, nearly all patients presenting with acute or chronic kidney disease of unknown etiology should undergo ultrasonography, the modality of choice to assess possible obstructive disease. Helical CT scan is generally preferred with patients with flank pain and possible urolithiasis. Among patients with moderate to advanced

by mansdocs.com

kidney disease with estimated GFR less than 30 mL/min, the administration of gadolinium has been associated with the potentially severe syndrome of nephrogenic systemic fibrosis. Most reported cases have been in chronic dialysis patients, but the syndrome may also occur in AKI.

RENAL BIOPSY

Renal biopsy is reserved for patients in whom prerenal and postrenal causes of AKI have been excluded and the cause of intrinsic renal injury is unclear. Renal biopsy is particularly important when clinical assessment and laboratory investigations suggest a diagnosis that requires confirmation before disease specific therapy (e.g. immunosuppressive medications) is instituted. Renal biopsy may need to be performed urgently in patients with oliguria who have rapidly worsening AKI, hematuria, and red blood cell casts. In this setting, in addition to indicating a diagnosis that requires immunosuppressive therapy, the biopsy may support the initiation of special therapies, such as plasmapheresis, if Goodpasture syndrome is present.

by mansdocs.com

CHAPTER

31

Renal Replacement Therapy

Rajesh Pande

INTRODUCTION

Kidney is a very vital organ and performs many important functions (Table 1).

Acute renal failure (ARF) presents a major therapeutic challenge for critical care physician. It is characterized by sudden decline in glomerular filtration rate (GFR), kidney's ability to eliminate waste products through glomerular filtration and leads to accumulation of urea and creatinine, decrease in urine output, metabolic acidosis, hyperkalemia and hyperphosphatemia. About 15–20% of intensive care unit (ICU) patients develop ARF during their stay and about 5% of patients require dialysis. The common causes of ARF in ICU are sepsis, shock, contrast and nonsteroidal anti-inflammatory drug (NSAID)-induced nephropathy.

Although there are many ways to classify ARF, the Second International Consensus Conference of the Acute

Table 1: Function and dysfunction of kidney.

Function	*Dysfunction*
• Salt, water and acid-base balance	• Salt, water and acid-base balance
– Water balance	– Fluid retention and hyponatremia
– Sodium balance	– Edema, CHF, hypertension
– Potassium balance	– Hyperkalemia
– Bicarbonate balance	– Metabolic acidosis, osteodystrophy
– Magnesium balance	– Hypermagnesemia
– Phosphate balance	– Hyperphosphatemia and osteodystrophy
• Excretion of nitrogenous end products	• Excretion of nitrogenous end products
– Urea	– Anorexia, nausea, pruritus, pericarditis, polyneuropathy, encephalopathy
– Creatinine	
– Uric acid	– Encephalopathy, thrombocytopathy
– Amines	
– Guanidine derivative	
• Endocrine-metabolic	• Endocrine-metabolic
– Conversion of vitamin D to active metabolite	– Osteomalacia, osteodystrophy
– Production of erythropoietin	– Anemia
– Renin	– Hypertension

(CHF: Congestive heart failure).

by mansdocs.com

Dialysis Quality Initiative (ADQI) Group developed a consensus definition for ARF in critically ill patients (RIFLE criteria) based on changes in the patients' GFR and/or their urine output. RIFLE is an acronym for risk of renal dysfunction, injury to the kidney [acute renal injury (ARI)], failure of the kidney (ARF), loss of kidney function and end-stage kidney disease. RIFLE criteria given are quite acceptable and validated in many studies (Fig. 1).

Preventive strategies for ARF are used by intensivist across the globe. Vigorous fluid repletion is very useful in prevention of ARF in situations like use of radio contrast agents, cisplatinum, amphotericin B, methotrexate, sulfonamides and acyclovir. Use of saline along with mannitol diuresis in crush syndrome and optional fluid hydration before major surgery.

Treatment could be pharmacological initially when the injury is minor but invariably requires dialysis in a large majority of patients. In severe ARF, extracorporeal techniques of blood purification [renal replacement therapies (RRTs)] must be applied to prevent complications. The various types of RRT's include: continuous hemofiltration, peritoneal dialysis and new hybrid techniques, like sustained (slow) low-efficiency daily dialysis (SLEDD).

Renal replacement therapy removes unwanted water and solute through a semipermeable membrane which could be either biological-peritoneum or artificial (hemodialysis or hemofiltration membranes). Hemodialysis causes hemodynamic instability whereas peritoneum dialysis has its limitations and cannot be used in hypotensive patients and is associated with risks. Continuous renal replacement therapy (CRRT) or SLEDD minimizes these effects.

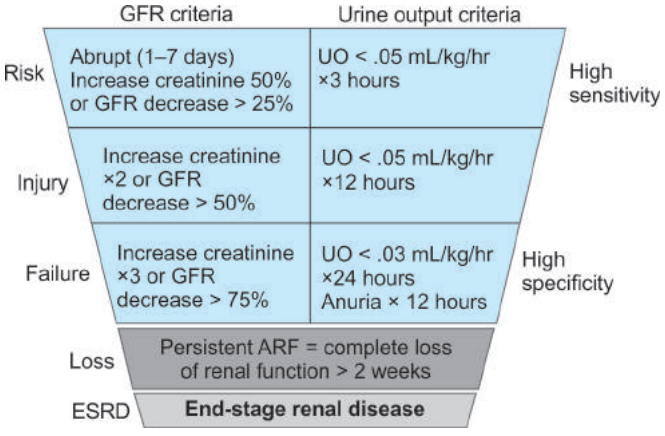


Fig. 1: Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria. (GFR: Glomerular filtration rate; ARF: Acute renal failure).

We often hear words like CRRT/intermittent hemodialysis (IHD)/SLED and there is a lot of confusion about what is best? Quite often we hear intensivist exclaim—I do not have a CRRT machine. Is my renal care suboptimal? The answer is somewhat complicated and requires a little understanding of the evolution of dialysis.

Dialysis started with extended dialysis (WJ Koff) on Sept. 11, 1945, and a patient named Maria was dialyzed for 11.5 hours, using blood flow rate of 116/min. With time technical complexities of dialysis machine increased and treatment time was shortened to increase efficiency of equipment. Therefore, length of session was abandoned. Short intermittent dialysis was established, but it was associated with problems like hemodynamic instability and fluctuating levels of fluid and electrolytes. To encounter this problem, CRRT was developed by P Kramer and colleagues from Gottingen.

Therefore CRRT, especially continuous venovenous hemofiltration (CVVH) become quite popular in ICU. But CRRT also had issues like limited capacity to remove nephrotoxins. To improve solute clearance, the convective principles of hemofiltration were combined with diffusive transport of dialysis and the process was called continuous arteriovenous hemodialysis (CAVHD) or hemofiltration. It is currently believed to be the most effective RRT for treating ARF in ICU.

Type	*Complex*	*Efficiency*	*ECF vol.*	*Low BP*
PD	+	++	++	yes
HD	++	+++	intermittent	no
CRRT	++/+++	++/+++	+++	yes

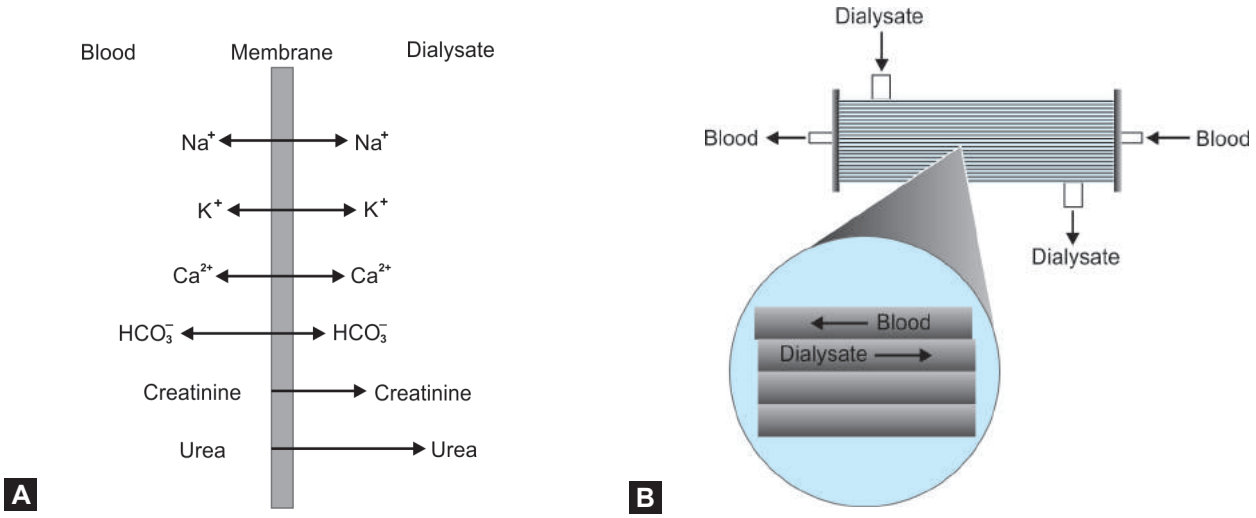
(HD: Hemodialysis; PD: Peritoneal dialysis; CRRT: Continuous renal replacement therapy; ECF: Extracellular fluid; BP: Blood pressure).

INDICATIONS

The indications for starting CRRT include:

- Anuria (no urine output for 6 hours)
- Oliguria (urine output < 200 mL/12 hours)
- Blood urea nitrogen (BUN) > 80 mg/dL or Urea > 28 mmol/L
- Creatinine > 3 mg/L or > 265 µmol/L
- K > 6.5 mmol/L or rapidly rising
- Pulmonary edema unresponsive to diuretics
- Uncompensated metabolic acidosis (pH < 7.1)
- Temperature > 40°C
- Uremic complications (encephalopathy, myopathy, neuropathy, pericarditis)
- Overdose with a dialyzable toxin (e.g. lithium)

by mansdocs.com



Figs. 2A and B: (A) Diffusion across a semipermeable membrane; (B) Process of diffusion.

Conceptually CRRT should be able to maintain homeostasis at all levels (water, electrolytes, blood pressure, acid-base status) and uremic control. The appropriate target urea is 20 mmol/L with a protein intake of about 1.5 g/kg/d, which can be achieved with CRRT at urea clearance of 30–40 L/d.

PRINCIPLES OF RENAL REPLACEMENT THERAPY

Ultrafiltration

It is a process by which water is transported across a semipermeable membrane and is used for fluid removal. The driving pressure is known as transmembrane pressure gradient and is the difference between plasma oncotic pressure and hydrostatic pressure. The determinants of ultrafiltration (UF) rate are membrane function area, water permeability of membrane and transmembrane pressure gradient (Figs. 2A and B).

Diffusion

It is the movement of solutes from high concentration area to low concentration area across a semipermeable membrane. This is facilitated by running dialysate countercurrent to blood flow. Solutes with high concentration in blood, e.g. urea, K^+ move across a membrane to the dialysate (Figs. 2A and B). Conversely solutes with high concentration in dialysate such as HCO_3, diffuse into the blood. Smaller solutes like urea diffuse more rapidly than larger solute.

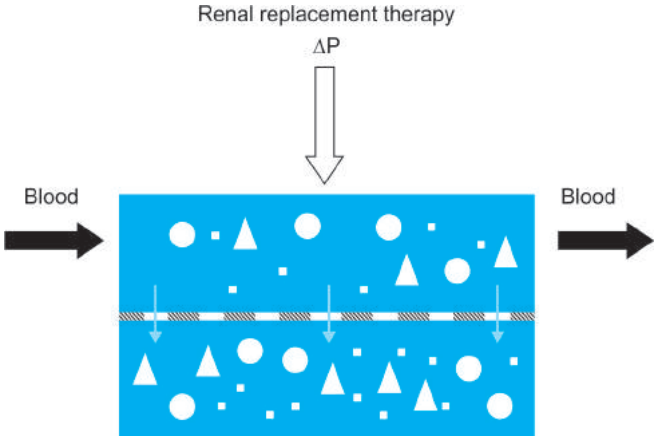


Fig. 3: Principle of convection.
(ΔP, pressure gradient; solid black arrow, direction of blood flow; squares, water molecules; circles and triangles, solutes; white arrows, movement of solute with water across a semipermeable membrane).

Convection

The transmembrane pressure gradient drives water across a semipermeable membrane (as in UF) but then drags with the water both small molecular weight solutes (BUN, Cr, K) and large molecular weight solutes [inulin, tumor necrosis factor (TNF), vit B12, β2 microglobulin] (Fig. 3). The efficiency of solute removal depends mainly on UF rate; at least 1 L of water needs to be pulled out across the membrane each hour. This process of increasing UF rate to facilitate convective clearance of solutes is known as hemofiltration (Fig. 4).

by mansdocs.com

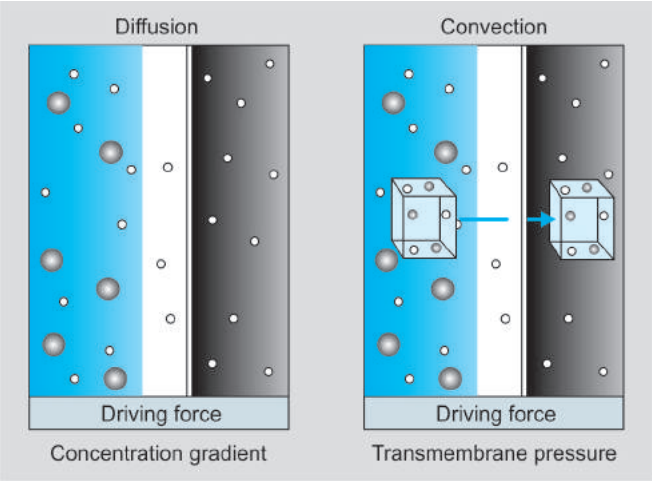


Fig. 4: Mechanism of solute removal.

Intermittent Hemodialysis

Standard IHD uses high dialysate flows (300–400 mL/min). It generates dialysate by using purified water and concentrate. It is applied for short periods (3–4 hours). But since volume has to be removed over short periods, it is poorly tolerated and may cause hypotension. Repeated hypotensive episodes may further delay renal recovery. Solute removal is episodic, resulting in inferior uremic and acid-base controls.

RECOMMENDATIONS FOR SYSTEMATIC USE

- Use only modified cellulosic membranes in place of cuprophane
- Simultaneously connect both lines of the circuit filled with 0.9% saline to the catheter
- Set dialysate sodium concentration more than 145 mmol/L
- Limit the maximal blood flow at 150 mL/min with minimal session duration of 4 hours
- Set dialysate temperature less than 37°C.

Advice for the Most Hemodynamically Unstable Patients

- Start session by dialysis and continue with UF alone
- Cool dialysate at 35°C.

Additional Recommendations

- Stop vasodilator therapy

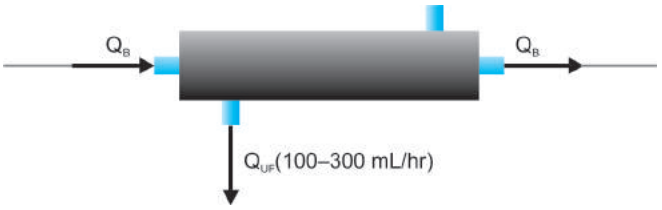


Fig. 5: Principle of slow continuous ultrafiltration. (Q_B: Blood flow rate; Q_{UF}: Ultrafiltration rate).

- Start session without UF, then adapt UF/hour rate according to hemodynamic response
- Strictly adapt UF order to patient's volemia and weight loss requirement.

WHAT IS BEST FOR ICU?

There is a great deal of controversy due to lack of randomized controlled trials comparing different techniques with sufficient statistical power. The techniques may be judged on the basis of hemodynamic side effects, ability to control fluid status, uremia, and avoidance of cerebral edema, ability to allow full nutritional support, control acidosis, and maintain electrolyte, phosphate and calcium homeostasis. Besides all these it should be biocompatible, minimize risk of infection and be cost effective.

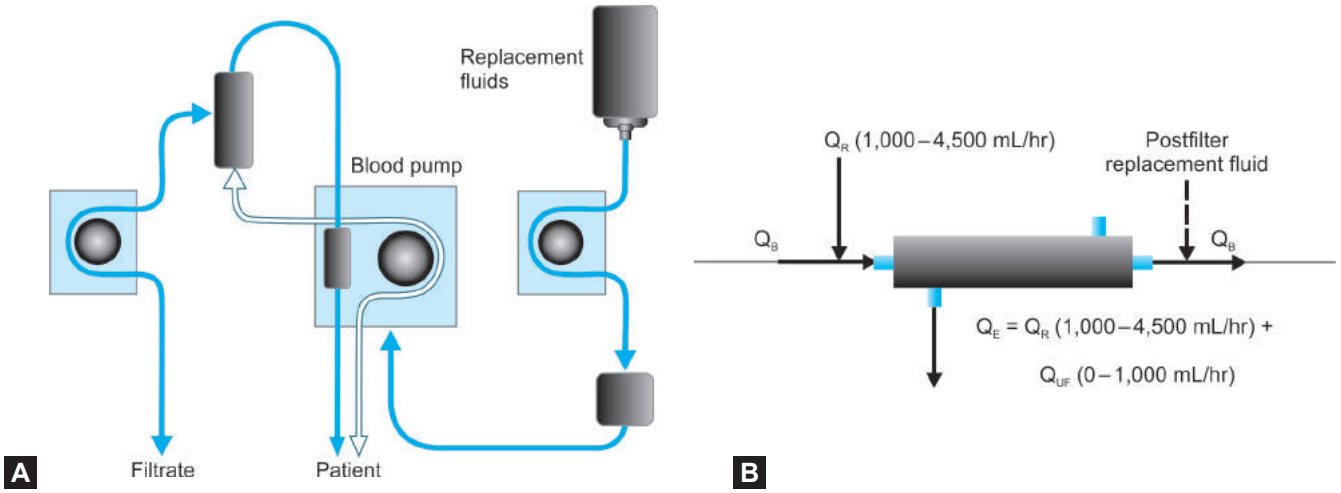
Slow Continuous Ultrafiltration

It is low-volume UF at a rate of 100–300 mL/hr is performed to maintain fluid balance only (Fig. 5). It does not result in significant convective clearance of solutes and no fluids are administered either as dialysate or replacement fluids. The indications are volume overload with or without renal failure, volume overload in patients with congestive heart failure refractory to diuretics.

Continuous Venovenous Hemofiltration

Here solute clearance occurs by convection. The solutes are carried along with the bulk flow of fluid in a hydraulic-induced ultrafiltrate of blood. No dialysate is used. Clearances are similar for all solutes that have a molecular weight in the range to which the membrane is readily permeable. The hourly UF rates of 1–2 L/hr are used to provide adequate solute removal. These high UF rates rapidly cause volume contraction, hypotension, and loss of electrolytes. Intravenous "replacement fluid" is provided to replace the excess volume that is being removed and replenish desired solutes (Figs. 6A and B). The replacement fluid can be administered either prefilter or postfilter.

by mansdocs.com



Figs. 6A and B: (A) Continuous venovenous hemofiltration; (B) Principle of continuous venovenous hemofiltration. (Q_B: Blood flow rate; Q_E: Effluent flow rate; Q_R: Replacement fluid flow rate; Q_{UF}: Ultrafiltration flow rate).

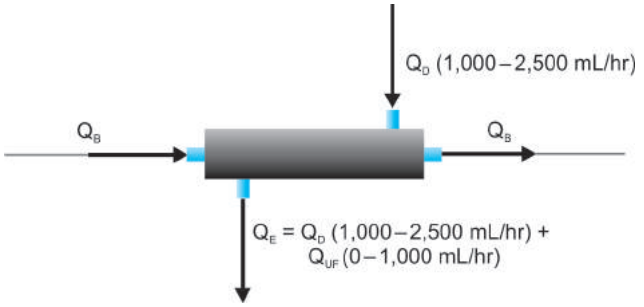


Fig. 7: Principle of continuous venovenous hemodialysis. (Q_B: Blood flow rate; Q_E: Effluent flow rate; Q_{UF}: Ultrafiltration flow rate; Q_D: Dialysate flow rate).

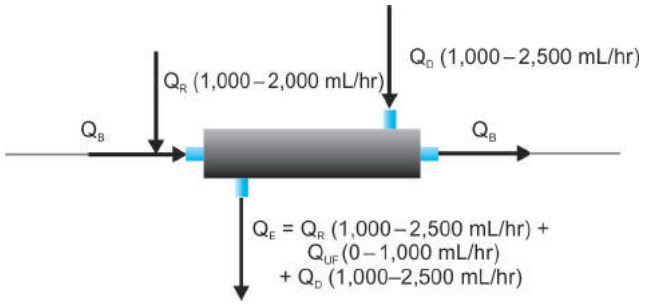


Fig. 8: Principle of continuous venovenous hemodiafiltration. (Q_B: Blood flow rate; Q_E: Effluent flow rate; Q_R: Replacement fluid flow rate; Q_{UF}: Ultrafiltration flow rate; Q_D: Dialysate flow rate).

Continuous Venovenous Hemodialysis

Here a dialysate solution runs counter current to the flow of blood at a rate of 1–2.5 L/hr (Fig. 7). Solute removal occurs by diffusion. Unlike IHD, the dialysate flow rate is slower than the blood flow rate, allowing small solutes to equilibrate completely between the blood and dialysate. As a result, the dialysate flow rate approximates urea and creatinine clearance. Ultrafiltration is used for volume control but can allow for some convective clearance at high rates.

Continuous Venovenous Hemodiafiltration

Continuous venovenous hemodiafiltration combines the convective solute removal of CVVH and the diffusive-solute removal of CVVH (Fig. 8). As in CVVH, the high UF rates used to provide convective clearance require the administration of intravenous replacement fluids. Replacement fluids can be administered prefilter or postfilter. Postfilter replacement fluid results in hemoconcentration of the filter and increased risk of clotting, especially when the filter fraction is greater than 30%. The filtration fraction is the ratio of UF rate to plasma water flow rate and is dependent on blood flow rate and hematocrit. Prefilter replacement fluid dilutes the blood before the filter, resulting in reduced filter clotting. Dilution of solutes before the filter reduces solute clearance by up to 15% by lowering the diffusion driving force and convective concentration.

Slow Low Efficiency Daily Dialysis

It is delivered as intermittent therapy but is less intense than normal HD (lower dialysate flow) therefore is given for longer duration (8 hours) and more frequently (daily).

by mansdocs.com

Advantages of Continuous Renal Replacement Therapy

Better hemodynamic tolerance due to slower UF. The gradual continuous volume removal makes control of volume status easier and allows administration of medications and nutrition with less concern for volume overload. Because it is a continuous modality, there is less fluctuation of solute concentrations over time and better control of azotemia, electrolytes, and acid-base status. The improved hemodynamic stability may be associated with fewer episodes of reduced renal blood flow, less renal ischemia, and more rapid renal recovery. Because CRRT does not cause rapid solute shifts, it does not raise intracranial pressure like IHD. The cumulative solute removal with CRRT is greater than that achievable with IHD. There are also several theoretical non-renal advantages of CRRT. It can remove toxins with a large volume of distribution and slow back diffusion from tissue into the circulation (e.g. methotrexate and procainamide). The ability of convective CRRT modalities to clear larger-molecular-weight molecules (up to 30,000 D) suggests that it may be beneficial in patients with sepsis or multiorgan failure. Experimental and clinical data show that many middle molecules, such as TNF, that may be involved in the inflammatory response can be removed by CRRT.

Disadvantages of Continuous Renal Replacement Therapy

Access and filter clotting, and the consequent need for anticoagulation are issues of concern. CRRT should ideally run with minimal interruption. Filter clotting may seriously compromises solute clearance, maintenance of electrolyte and acid-base balance, and volume management. Platelet microthrombi and leukocyte-platelet aggregates may clot the dialyzer membrane. Unfractionated heparin has been the mainstay of anticoagulation for prevention of dialyzer filter clotting, but is associated with a 30% risk of life-threatening bleeding and the development of heparin-associated antibodies. Increased cost and demands on ICU nurse time compared with IHD. It may be difficult to perform interventions and do procedures. The incidence of pressure sores may increase due to prolonged position in supine posture.

CRRT is gaining greater acceptance with the use of venovenous access and its advantages in hemodynamically unstable patients. IHD is best for patients requiring rapid metabolic control (e.g. in hyperkalemia), whereas volume overload is best managed with CRRT. Hemodynamically unstable patients/or who have increased intracranial pressure are best treated with CRRT. Patients in whom anticoagulation is contraindicated might be better managed with IHD unless CRRT with citrate is used. CRRT is limited by its greater cost and demands on nursing time and the constraint it places on a patient's mobility. The choice of RRT depends on the underlying disease and etiology of ARF, but this question requires further study. The choice of modality should be based on the clinical status of the patient, the resources available in the institution, and the cost of therapy.

by mansdocs.com

CHAPTER

32

Critical Care Management of Renal Transplant Recipients

Sachin Gupta, Deepak Govil

INTRODUCTION

Renal transplant should be considered for all chronic kidney disease (CKD) patients as patients have a better quality of life with improved survival as compared to long-term dialysis. The renal transplant recipient has specific postoperative issues which should be taken into consideration when dealing with them in intensive care unit (ICU). The general principle of ICU management of kidney recipient is to ensure adequate hemodynamic stability, monitor for any side effects of drugs like immunosuppressants and keep a close watch on any sign of infection or rejection.

HEMODYNAMIC STABILITY

All recipients should have an ECG and invasive arterial line in situ in the immediate postoperative period.These patients should be monitored for adequate urine output which should range from 0.5 mL/kg/h to 1 mL/kg/h for first 24 hours. Volume status should be assessed with the help of dynamic indices like continuous central venous pressure (CVP) monitoring, inferior vena cava collapsibility assessment by repeated USG examinations and looking for signs of adequate organ perfusion like decreasing lactate clearance.

The aim of fluid management in recipients should be to make them hypervolemic in the initial postoperative period. Patients should receive 0.45% NS as replacement fluid during first postoperative day. This replacement fluid should be given as 100% replacement amount equal to hourly urine output of the patient. Apart from this, patient should also receive maintenance fluid to account for other fluid losses like nasogastric tube drainage, loose motions, loss in the drains and insensible losses.

If the urine output is low in the immediate postoperative period, one should first look for mechanical cause like obstruction of the urinary catheter by a clot or kinking of the catheter because increase in intravesical pressure may compromise the newly created anastomosis between the vesicles and bladder. Patients may have hematuria due to bleeding from the ureteral anastomosis, from bladder or along the urethra. The catheter should be first "milked" to dislodge the clot. The catheter can also be gently flushed with 20–30 mL saline to remove the clots. Even the catheter can be converted to three-way catheter for continuous irrigation to dilute the hematuria.

If urine output is still low, then diuretics like furosemide can be tried. Hypotension should be avoided in such patients as good percentage of CKD patients are hypertensive preoperative and require a high driving pressure for urine production. No particular vasopressor agent is preferred and the general choice remains the same as for any other hypotensive patient in the ICU. Generally, noradrenaline is the first choice of vasopressor agent. Low dose dopamine which was also labeled as "renal dose dopamine" has been used to increase the intravesical pressure but has proved to increase the mortality due to more arrhythmogenic potential. The CKD patients are more prone to cardiac disorders preoperatively and so dopamine should be avoided in these patients.

by mansdocs.com

If diuretic trial fails, then Doppler scan of the newly grafted kidney should be done to look for vascular occlusion or hydronephrosis. If Doppler scan is normal and urine output does not increase then consider acute tubular necrosis or hyperacute rejection and patients may require renal replacement therapy.

INFECTION PROPHYLAXIS

Infection in the post-transplant period is one of the most important predictor of increased morbidity and mortality. All transplant recipients are at an increased risk of nosocomial infections due to poor immune status because of chronic debilitating illness. These patients generally have poor nutritional status. They also have repeated hospital admissions preoperatively either for dialysis or for infections. They also have received multiple antibiotics during their preoperative period and so are candidates to harbor multidrug resistant organisms postoperatively.

Infections depend on the time elapsed from the transplant period. In the immediate postoperative period, infections are generally related to the surgical procedure, urinary tract infection, line sepsis and respiratory tract infection.

All recipients should receive antibiotics as per the hospital protocol but it generally includes antibiotics covering ESBL organism and having good renal penetration to prevent urinary tract infection. Prophylactic intravenous antifungal should be given for the initial postoperative period in high risk renal transplant recipients otherwise oral antifungal drops are given as a routine to all recipients for at least 1 month postoperatively. A high index of suspicion should be kept to identify subtle signs and symptoms of sepsis as these patients may not mount the same inflammatory response as other septic patients would do. Routine surveillance cultures like blood and urine cultures should be sent. Recipients receiving kidney from cytomegalovirus (CMV) positive donors have a high chance of contracting CMV infection in the postoperative period and should be empirically started on intravenous ganciclovir 95 mg/kg twice daily as induction dose for 1 week and then can be converted to oral valganciclovir 900 mg/day. Simultaneous CMV, DNA and polymerase chain reaction (PCR) should be sent and one should look copies of the virus.

GRAFT FUNCTION

Patients may have either early graft dysfunction or delayed graft dysfunction. In the early postoperative period, patients generally will have a slow decline of serum creatinine with persisting metabolic acidosis and occasionally hyperkalemia. These patients will require early renal replacement therapy within the 1 week of transplant. Hemodialysis or peritoneal dialysis can be done but generally in ICU settings, hemodialysis is a more justifiable option. The principles of dialysis remain the same as for any other patient. Rejection can be proved with the help of renal biopsy.

IMMUNOSUPPRESSANTS

As an intensive care physician, one should understand the basics of immunosuppressant drugs with some common side effects and interaction with other antibiotics. The commonly used drugs are calcineurin inhibitors (CNI), steroids and mycophenolate mofetil (MMF). CNI can cause drug induced nephrotoxicity and also has a potential to cause neurotoxicity like seizures or focal muscular twitchings. Steroids, as is known to cause hypertension and new onset diabetes mellitus, is an integral part of postoperative immunosuppression. MMF is a potent immunosuppressant. It should be given with caution if patient has thrombocytopenia. One should monitor the blood levels of CNI and alter the dosages as per the levels.

Certain drugs increase the drug level of CNI in blood. Drugs like amiodarone, verapamil, macrolide antibiotics, azole group, phenytoin, carbamazepine, cephalosporins and rifampicin.

CARDIOVASCULAR STABILITY

Renal transplant recipients are generally hypertensive in the post-transplant period and require an antihypertensive treatment. The target of blood pressure control is to keep systolic BP around 130 mm Hg. Calcium channel blockers are the choice of antihypertensive drugs. Other drugs like beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) should not be considered in the immediate postoperative period and can be started after 6 weeks of transplant.

Patients can also have fluid overload after transplant if there is graft failure with decreasing urine output. These

by mansdocs.com

patients would require an urgent dialysis support to decongest these patients.

OTHER SUPPORTIVE CARE

These patients are generally nutritionally depleted and should be encouraged to have high protein calorie rich diet. Routine physiotherapy should be conducted and both active as well as passive exercises should be instituted. Prophylaxis for deep vein thrombosis should be initiated once there is no evidence of postoperative bleeding. Till that time compression stockings should be applied.

Renal transplant recipients generally have a shorter stay in ICU and if there is uneventful surgical period, the outcome of these patients is favorable. The role of intensivist in managing these patients is critical as the early phase of postoperative period is labile and if adequate perfusion and volume status is not maintained, then graft injury is a possibility.

by mansdocs.com

CHAPTER

33

Acid-Base Disorders in Critical Care

Palepu B Gopal, Krishna Prasad Mulavisala

INTRODUCTION

Patients admitted in intensive care units (ICUs) have frequently vital organ dysfunction and not infrequently multiorgan dysfunction or even failure. These phenomena do exert their influence on acid-base balance of human body. These patients also have a high incidence of comorbidities involving various organs vital for acid-base homeostasis, and consequently suffer from pre-existing disturbance in acid-base balance. To add to these complexities, polypharmacy is an integral part of critical care therapy, which can further impact acid-base balance. These imbalances have a propensity to become a vicious cycle and significantly influence the progress and outcome of critically sick patients. So, it becomes imperative for the intensivist to understand, prevent, minimize and treat the acid-base imbalances occurring in a critically sick patient.

PHYSIOLOGY OF ACID-BASE HOMEOSTASIS

Diagnosis of acid-base status warrants simultaneous analysis of arterial blood gas (ABG), serum electrolytes and osmolarity, and urine analysis. Anion gap (AG) estimation is mandatory on every blood gas studied, as it will reveal high AG metabolic acidosis and a hidden mixed disorder even in otherwise normal looking ABG. Buffers, both intra- and extracellular, along with respiratory and renal regulatory systems maintain pH of human blood in the normal range of 7.35–7.45. Respiratory system, governed by central nervous system (CNS) controls partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and bicarbonate is under the control of kidneys, through retention or excretion of acid or alkali. The routinely followed HCO_3^- based Henderson and Hasselbalch equation for regulation of pH encompasses the respiratory and metabolic components and is:

$$pH = pK_a + \log_{10} HCO_3^- / PaCO_2 \times 0.0301$$

Changes in $PaCO_2$ may be due to ventilatory dysfunction of lungs or as a compensatory response to changes in serum HCO_3^-. Renal system maintains pH by either reabsorption of filtered HCO_3^- or generation of new HCO_3^- or ammonia (NH_3) excretion. *Acidemia and alkalemia* are decrease and increase in systemic pH, respectively. *Acidosis and alkalosis* refer to such changes occurring in pH as a consequence of changes in $PaCO_2$ or HCO_3^-. Respiratory ($PaCO_2$) or renal and/or metabolic (HCO_3^-) dysfunctions attempt to alter pH, resulting in primary acidosis or alkalosis. This evokes secondary changes in the other system leading to compensatory alkalosis or acidosis. So, the pH is regulated in normal range of 7.35 –7.45, either by $PaCO_2$ regulation through respiratory mechanisms, or regulation of HCO_3^- by kidneys, or both. There is also a more recent H^+ concentration based strong ion concept proposed by Stewart, which is less routinely followed. It can be of help in solving some of the more complex acid-base disorders due to unmeasured ions not included in routine investigations.

ANALYSIS OF DISORDERS OF ACID-BASE BALANCE

Altered pH will guide as to the nature of disturbance in simple abnormalities, and $PaCO_2$ or HCO_3^- will denote the

by mansdocs.com

Table 1: Estimation and validation of compensatory responses to simple acid-base disorders.

Primary acid-base disorders	*Compensatory response*	*Estimation of expected compensation*	*Compensation limits*
Respiratory acidosis	Increased renal HCO_3^- reabsorption (HCO_3^- ↑)	*Acute*: Δ[HCO_3^-] = +1 mEq/L for each ↑ΔPCO_2 of 10 mm Hg	[HCO_3^-] = 38 mEq/L
		Chronic: Δ[HCO_3^-] = +4 mEq/L for each ↑ΔPCO_2 of 10 mm Hg	[HCO_3^-] = 45 mEq/L
Respiratory alkalosis	Decreased renal HCO_3^- reabsorption (HCO_3^- ↓)	*Acute*: Δ[HCO_3^-] = –2 mEq/L for each ↓ΔPCO_2 of 10 mm Hg	[HCO_3^-] = 18 mEq/L
		Chronic: Δ[HCO_3^-] = –5 mEq/L for each ↓ΔPCO_2 of 10 mm Hg	[HCO_3^-] = 15 mEq/L
Metabolic acidosis	Alveolar hyperventilation to increase pulmonary CO_2 excretion (↓ PCO_2)	PCO_2 = 1.5 [HCO_3^-] + 8 ± 2 PCO_2 = last 2 digits of pH × 100 PCO_2 = 15 + [HCO_3^-]	PCO_2 = 15 mm Hg
Metabolic alkalosis	Alveolar hypoventilation to decrease pulmonary CO_2 excretion (↑PCO_2)	PCO_2 = + 0.6 mm Hg for Δ[HCO_3^-] of 1 mEq/L. PCO_2 = 15 + [HCO_3^-]	PCO_2 = 55 mm Hg

origin and compensation, but complex and mixed defects will need further analysis. Acid-base disorders can be:

- *Acidosis* (Low pH): Metabolic (low HCO_3^-) or respiratory (high $PaCO_2$)
- *Alkalosis* (High pH): Metabolic (high HCO_3^-) or respiratory (low $PaCO_2$)

Mixed acid-base abnormalities.

There are several methods to estimate the compensatory response to primary disorder. While there are some standard formulae in practice (Table 1), there are also some proposed acid-base nomograms (Fig. 1).

Extremes of pH seen in many critically sick patients are due to independent acidosis and/or alkalosis coexisting with each other, and are not simply compensatory to the primary disorder. These may be due to either primary or superimposed disease of a system or reflection of another failing organ system as part of multiorgan failure, which is common in ICU. Patients with chronic respiratory disorders, chronic renal failure (CRF) drug ingestion, and diabetic ketoacidosis (DKA) give rise to such complex disorders. In the face of normal pH in such conditions, AG may give clue to the true nature of acid-base disorder.

HOW DO YOU DIAGNOSE ACID-BASE DISORDERS?

Arterial blood gas analyzers measure pH and $PaCO_2$, and then calculate HCO_3^-. This calculation can be validated by comparing with measured HCO_3^- or total CO_2 obtained from laboratory, along with electrolytes. It is necessary to keep the patient's clinical profile and the underlying disease syndrome in view while deciding if the ABG shows either acidosis or alkalosis. The acid-base shift has significant implications to electrolyte status, especially for potassium.

LOW ARTERIAL BLOOD pH

METABOLIC ACIDOSIS

Clinical Aspects of Metabolic Acidosis

Eliciting history of diabetes mellitus, alcoholism, renal failure and drug ingestion is essential. Systemic examination for signs of uremia, conditions giving rise to lactic acidosis such as shock states and cancers will lead to therapeutic options.

Acidosis has many systemic effects, some of which help in diagnosis and some may be life threatening. Decreased myocardial contractility, tachyarrhythmias with venoconstriction and arterial dilatation, along with decreased response to catecholamines pose a challenge. Patient may become dyspneic due to increased minute ventilation (Kussmaul respiration) leading to respiratory fatigues, which may necessitate ventilation. Decreased cerebral metabolism will be evidenced as obtundation

by mansdocs.com

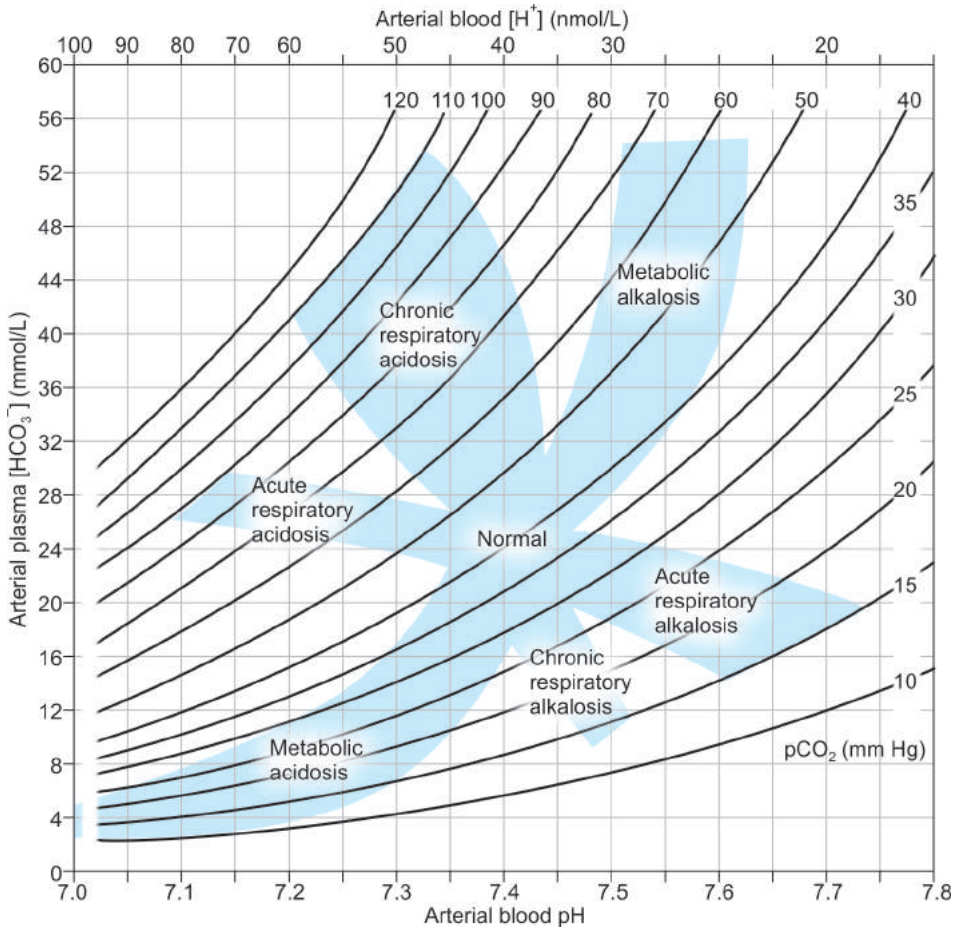


Fig. 1: Acid-base nomogram

ABG derived pH, HCO_3 and $PaCO_2$ can be plotted on this nomogram grid. Shaded areas represent 95% confidence limits of normal respiratory and metabolic compensations for primary disturbances. Points outside shaded areas represent a mixed disorder.

and coma, while there may also be hyperactivity of sympathetic nervous system. Hyperkalemia may become life threatening along with hyperphosphatemia and increased protein catabolism.

In the general management of metabolic acidosis, etiology has to be targeted. Alkali administration has no proven value and outcome benefit in critically ill, except when, there is evidence of:

- Severe acidemia with no potential HCO_3^- in plasma (pH < 7.15)
- Non-gap hyperchloremic acidosis
- Mixed mild AG and mixed hyperchloremic acidosis, and
- High gap acidosis of renal failure.

The target of alkali therapy should be a maximum pH of 7.25 and HCO_3^- rise to not more than 15 mEq/L, while watching for hypokalemia as pH is rising. On the other hand, it carries the risk of hypernatremia, hypercapnia, fluid overload, cerebrospinal fluid (CSF) acidosis and overshoot alkalosis.

Anion Gap

The next step is to calculate AG and is the key to diagnose acid-base disorders.

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

The normal value of AG is 9 ± 3 mEq/L, because the total unmeasured anions exceed the total unmeasured cations. K^+ value being in a single digit is ignored. AG has to be corrected upwards with a factor of 2.5 for every 1 gram drop of albumin below its normal value of 4.5 g/dL. Corrected AG can also be calculated as *Expected AG = 2 (albumin g/dL) + 0.5 (phosphate mg/dL)*.

by mansdocs.com

Osmolar Gap

Estimation of osmolar gap in addition to AG is helpful in diagnosing acidosis caused by certain agents. The calculated and measured (laboratory) plasma osmolarity should be within 15 mOsm/kg.

Osmolarity can be calculated by: $P_{osm} = 2Na^+ + Glu$ (mg/dL) / 18 + Blood urea nitrogen (BUN) (mg/dL) / 2.8

High osmolar gap denotes either spurious hyponatremia or proportionate presence of other hyperosmolar agents in plasma, such as mannitol, contrast media, alcohols or acetone.

HIGH AG METABOLIC ACIDOSIS

Increased AG acidosis is very common in ICU when non-Cl^-, non-HCO_3^- anions increase. Common conditions giving rise in organic anions are lactic acidosis, ketoacidosis, uremic acidosis and toxins. High albumin concentration, rise in inorganic phosphates and sulfates during alkalosis also have to be considered. Unidentified anions during hyperosmolar nonketotic states, myoglobinuria and decrease in Ca^{2+} and Mg^{2+} have to be taken into account.

Decreased AG is seen when there is increase in non-Na^+ cations such as Ca^{2+}, Mg^{2+}, Li^+ and IgG (in gammopathies) or decrease in non Cl^-, non HCO_3^- anions such as albumin, or rarely iodide, and bromism, and in hyperviscosity syndromes.

The cardinal feature of high AG acidosis is low HCO_3^-. The exception to this will be a coexisting chronic respiratory acidosis or evolving metabolic alkalosis where in the face of high AG, HCO_3^- will be normal or even elevated. These are mixed disorders. One needs to estimate adequacy of compensatory responses at this stage, utilizing one of the formulae given in Table 1. The relationship of ΔAG to ΔHCO_3^- (Gap-gap) is important, which will reveal concealed disorders. The ratio of ΔAG to Δ HCO_3^- values is usually 1 in pure high AG acidosis. A ratio of more than 1 suggests mixed metabolic acidosis plus metabolic alkalosis and a ratio of less than 1 suggests presence of mixed gap plus non-gap acidosis.

Lactic Acidosis—Causes and Management

More than 60% of critically ill patients suffer from lactic acidosis. Lactic acidosis was divided into type A and type B, by Hukabee and Kohen, and further due to L-lactate and D-lactate (Table 2). L-lactate is the product of anaerobic metabolism of pyruvate, which in turn is a product of glucose in Embden-Meyerhof pathway. Liver and kidney (Cori's cycle) reconvert lactate to pyruvate, and this process is deranged in hypoperfusion states. Ideally pyruvate:lactate ratio would be more pertinent, but pyruvate cannot be measured. A serum L-lactate level of more than 4 mEq/L is clinically significant and denotes high mortality and warrants clinical intervention.

Catecholamines add to lactic acidosis by stimulating cellular metabolism in face of oxygen deficit. D-lactate acidosis is associated with hyperchloremia and is seen in overgrowth of gut bacteria. Patients in sepsis, congestive heart failure (CHF), renal dysfunction and liver dysfunction may develop lactic acidosis due to metformin therapy, which should be avoided. Carbon monoxide causes lactic acidosis by reducing oxygen carrying capacity of hemoglobin. Propylene glycol, which is a carrier in benzodiazepines can accumulate and cause high AG acidosis with prolonged infusions.

Rapid lactate clearance has shown to improve outcome in such situations by Falk and associates. Key to managing lactic acidosis is etiological correction of the shock causing hypoperfusion and hypoxemia and optimizing oxygen carrying capacity of blood, which leads to reduced lactate production and reverses acidosis. Correction of pH by administering $NaHCO_3$ is common, but has several deleterious effects, such as fluid and sodium overload, central vasoconstriction, reduced cardiac output, overshoot alkalosis and paradoxical intracellular acidosis. It may also cause hyperosmolarity, hypokalemia and hypercarbia in face of respiratory failure. However, it is reasonable to combat severe acidosis with $NaHCO_3$ administration with a target of raising pH to 7.2 and HCO_3^- to not more than 15 mEq/L. Dichloroacetate and Tromethamine (Tham) have been tried to neutralize acidosis without any outcome benefit.

Severe acidosis and fluid overload may however necessitate continuous renal replacement therapy (CRRT) especially if associated with renal dysfunction and hyperkalemia. CRRT with HCO_3^- solutions achieves a good acid-base and electrolyte balance, fluid volume management and possible endotoxin and mediator removal.

D-lactic acidosis should be suspected in patients with gut pathology with symptoms of acidosis but normal lactate levels. Treatment is aimed at limiting overgrowth of gut bacteria and avoidance of high carbohydrate alimentation.

Ketoacidosis

The one seen usually in diabetics with a stress state such as infection or myocardial infarction (MI) is

by mansdocs.com

Table 2: Causes of high anion gap and normal anion gap acidosis.

High anion gap

1. Ketoacidosis
   - Diabetic ketoacidosis (acetoacetate)
   - Alcoholic (β-hydroxybutyrate)
   - Starvation
2. Lactic acid acidosis
   - *L-Lactic acid acidosis*
     - *Type A lactic acidosis*:
       - Shock
         - Cardiogenic
         - Hemorrhagic
         - Septic
       - Profound hypoxemia (asthma, anemia)
       - Carbon monoxide poisoning
     - *Type B lactic acidosis*:
       - Liver disease
       - Diabetes mellitus
       - Excess endogenous and exogenous catecholamines
       - Thiamine deficiency
       - Ketoacidosis
       - Seizure
       - Malignancy
       - Intracellular inorganic PO_4 depletion
       - IV fructose, xylose and sorbitol
       - Mitochondrial toxins
       - Metformin
       - Pyroglutamic acid (Paracetamol)
   - *D-Lactic acid acidosis*
     - Short bowel syndrome
     - Ischemic bowel
     - Small bowel obstruction
3. Rhabdomyolysis
4. Renal failure
5. Toxin Ingestions
   - Ethylene glycol → glycolate, oxalate
   - Methyl alcohol → formate
   - Salicylate → ketones, lactate
   - Paraldehyde → organic anions
   - Toluene → hippurate
   - Propylene glycol → lactate

Normal anion gap

1. GI loss of HCO_3^- (negative urine anion gap)
   - Diarrhea
   - Fistula, external
2. Renal loss of HCO_3^- or failure to excrete NH_4^+
   - Proximal RTA (type 2)
   - Acetazolamide
   - Classic distal RTA (type 1)
   - Generalized distal RTA (type 4)
3. Miscellaneous
   - NH_4Cl ingestion
   - Sulfur ingestion
   - Dilutional acidosis
   - Late stages in treatment DKA

Source: Adapted and modified from DuBose TD Jr. Acid-base disorders. In: Brenner BM (Ed). Brenner and Rector's The Kidney, 8th edition. Philadelphia: Saunders; 2008, p.513-46.
*(*GI: Gastrointestinal; RTA: Renal tubular acidosis; DKA: Diabetic ketoacidosis).

DKA. Accumulation of ketoacids (acetoacetic and β–hydroxybutyric acids) acids due to increased fatty acid metabolism combined with insulin deficiency and/or resistance is the basic cause. Increased AG and severe hyperglycemia can be managed by IV insulin administration. 0.1 mg of regular insulin is given as an initial bolus dose followed by same dose as infusion in the first hour. Subsequent insulin dosage is guided by serum glucose levels.

Blood glucose, acid-base status and electrolytes have to be frequently monitored. Adequate fluid administration is essential, but may be limited by poor renal function. Normal saline is the fluid of choice at a rate of 1 L/hour. Na^+ levels have to be closely monitored and corrected according to serum glucose levels (correct Na^+ by 1.6–1.8 mEq/L for each 100 mg/dL increment in plasma glucose). When Na^+ level reaches 130–135 mEq/L and patient is stable, switch to 0.45% saline. But, recently DKA

by mansdocs.com

management with large volume fluid has been challenged. When a serum glucose level of 300 mg/dL is achieved, the fluid should be changed to 0.45% saline in 5% dextrose.

The total body potassium is low in DKA and the presenting K^+ values may be misleading. Administration of fluids, insulin and HCO_3^- further drops K^+ levels. Once good urine output has been established and if K^+ values are still below 4 mEq/L, cautious correction should be initiated. Extreme caution should be applied in case of renal dysfunction to avoid hyperkalemia.

Abrupt curtailment of alcohol in chronic malnutritioned alcoholics may precipitate severe ketoacidosis (high β–hydroxybutyric acid) and ketonuria with low or normal glucose. Abdominal pain and vomiting, chronic liver disease, mixed acid-base disorders with mild lactic acidosis frequently coexist and may lead to diagnostic confusion. High blood alcohol level will result in increased osmolar gap. Glucose in isotonic saline is the preferred treatment. Insulin should be avoided. Estimation and correction of phosphate, magnesium and potassium should be undertaken.

Acidosis Due to Toxin Ingestion

Salicylate intoxication leads to respiratory alkalosis, mixed metabolic acidosis plus alkalosis, or a pure high AG acidosis. Lactic acidosis with high ketones is also reported. Normal saline gastric lavage should be followed by activated charcoal administration. $NaHCO_3$ can be given to counter severe acidosis, which will also facilitate salicylate removal through alkalization of urine (pH > 7.5). Acetazolamide can be added to $NaHCO_3$. Hyponatremia, hypokalemia and hypoglycemia may complicate diuresis and need to be monitored and corrected. Severe salicylate poisoning will leave with no choice except hemodialysis, especially in the presence of renal failure.

Ethylene glycol ingestion, a component of antifreeze, leads to high AG, high osmolar gap acidosis and secondary lactic acidosis due to multiorgan collapse. Renal failure along with oxalate crystals in urine are typical features. Urgent saline therapy combines with osmotic diuresis, thiamine and pyridoxine supplements and administration of alcohol dehydrogenase inhibitor fomepizole or ethanol may lessen the toxicity. Eventual hemodialysis can remove ethylene glycol and its metabolites from blood. *Methanol* and its metabolites, formaldehyde and formic acid cause high AG and elevated osmolar gap acidosis leading to severe CNS and optic nerve damage with considerable mortality. Treatment is on standard lines mentioned for ethylene glycol. *Ethanol* by itself does not cause acidosis unless accompanied by hypotension. *Isopropyl alcohol* ingestion or skin absorption typically causes elevation of osmoalr gap but causes neither high AG nor low glucose and HCO_3^-. Standard therapy may be successful in many cases but severe intoxication may necessitate dialysis.

Paracetamol may rarely deplete glutathione and lead to excess formation of pyroglutamic acid or *5-oxoproline*. This is seen in a proportion of patients with sepsis, who exhibit high AG acidosis.

Acidosis Due to Renal Failure

This deserves special mention due to its high incidence in critically sick patients. Its initial presentation might be of hyperchloremic in nature, but eventually it attains a high AG acidosis when it progresses to advanced stage. Chronic uremic acidosis secondary to reduced NH_4^+ production results in moderate HCO_3^- acidosis with AG less than 20. Bone calcium loss will be evident due to loss of bone calcium carbonate and renal loss of calcium. Oral alkali supplementation will be required in CRF to maintain HCO_3^- above 20 mEq/L. This may translate to small amounts of IV bicarbonate therapy for critically ill patients. For patients in acute kidney injury or acute on chronic renal failure (CRF), dialysis may be the recourse with bicarbonate-based dialysates.

NORMAL AG METABOLIC ACIDOSIS

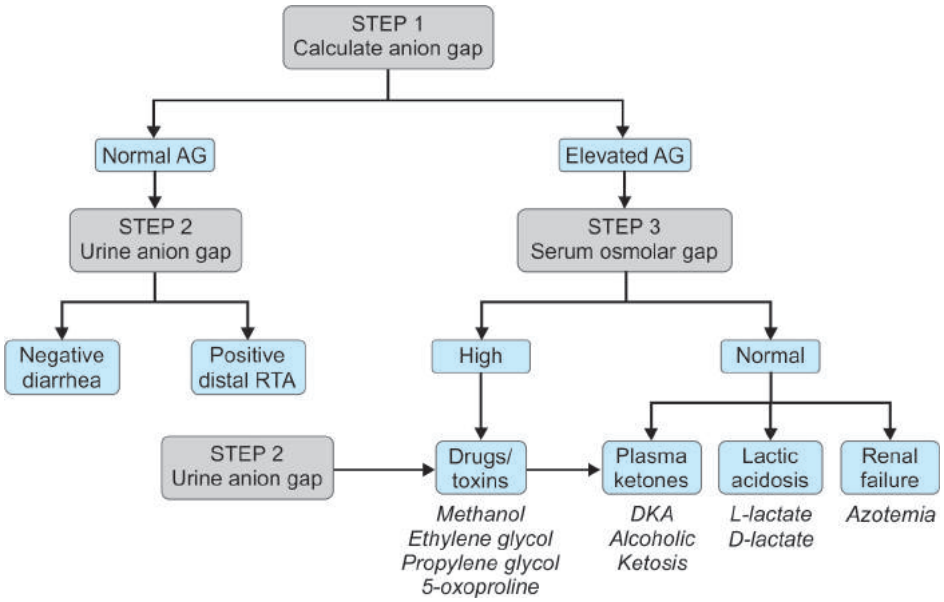
The AG does not increase in two main instances of loss of HCO_3^- through gastrointestinal tract (GIT) and kidneys, and leads to *non-anion gap acidosis*. Shifts in Cl^- have to be compared with that of Na^+ to diagnose hyperchloremic acidosis. Bicarbonate loss from lower GIT or kidneys gives rise of Cl^- and reduction of HCO_3^- levels, resulting in normal AG, hyperchloremic metabolic acidosis with low arterial pH. Hypokalemia is a feature of both these conditions. In this situation, urinary pH and urine anion gap (UAG) will differentiate between the two important causes of normal AG acidosis, i.e. UAG being negative in diarrhea (high urine pH) and UAG being positive in renal tubular acidosis RTA (low urine pH) (Flowchart 1). UAG is the net result of variable gap between urinary cations ($Na^+ + K^+$) and anions (Cl^-), due to excreted NH_4^+, which also influences urine pH. UAG is referred by some as urine strong ion difference (SID).

$$UAG = [Na^+ + K^+] - [Cl^-]$$

Hyperchloremic acidosis is either due to gastrointestinal HCO_3^- loss or renal acidosis. The later can be divided into hypo-, hyper- and normokalemic varieties (Table 3).

by mansdocs.com

Flowchart 1: Stepwise analysis for anion gap (AG) acidosis diagnosis.



Source: Adopted and modified from DuBose TD Jr. Acid-base disorders. In Brenner BM (Ed). Brenner and Rector's The Kidney, 8th edition. Philadelphia: Saunders; 2008.
(RTA: Renal tubular acidosis; DKA: Diabetic ketoacidosis).

Table 3: Hyperchloremic metabolic acidosis.

Gastrointestinal bicarbonate loss	
Diarrhea • External pancreatic or small bowel drainage • Ureterosigmoidostomy, Jejunal loop *Drugs*: – Calcium chloride (acidifying agent) – Magnesium sulfate (diarrhea) – Cholestyramine (bile acid diarrhea)	
Renal acidosis	
Hypokalemic • *Proximal RTA (type 2)* • Distal [classic RTA (type 1)] • Drug-induced hypokalemia: – Acetazolamide (Proximal RTA) – Amphotericin B (Distal RTA)	• Trimethoprim • Pentamidine • ACE inhibitors • Angiotensin II receptor blockers • NSAIDs • Cyclosporine, tacrolimus
Hyperkalemic • Generalized distal nephron dysfunction (type 4 RTA) • Mineralocorticoid deficiency or resistant pseudohypoaldosteronism type 1 ↓ Na^+ delivery to distal nephron • Tubulointerstitial disease • Ammonium excretion defect • Drug-induced hyperkalemia: K^+ sparing diuretic-amibride, triamterene, spironolactone	*Normokalemic* • Early renal insufficiency
Other causes	
• Acid loads (ammonium chloride hyperalimentation) • Loss of potential bicarbonate: ketosis with ketone excretion • Dilution acidosis (rapid saline administration) • Hippurate – Cation-exchange resins	• Dilution acidosis (rapid NaCl administration) • Hippurate – Cation-exchange resins

(RTA: Renal tubular acidosis; ACE: Angiotensin-converting enzyme; NSAIDs: Nonsteroidal anti-inflammatory drugs).

by mansdocs.com

Type 1 (classic distal) RTA is renal defect in acid excretion, due to limited ability of the collecting ducts to excrete acids (NH_4^+) in face of systemic acidosis. Hypokalemia, hyperchloremic acidosis, reduced urinary NH_4^+ excretion leading to positive UAG, and high urine pH are typical features of distal RTA. Calcium and citrate loss in urine will result in renal stones and nephrocalcinosis along with bone disease. Moderate doses of alkali therapy ($NaHCO_3$ 1–3 mEq/kg/day) will neutralize diet derived acids and will maintain neutrality. Attempt to correct acidosis with large doses of bicarbonate may precipitate severe hypokalemia (Table 4).

Proximal renal tubular acidosis (type 2 RTA) caused by generalized proximal tubular dysfunction and is manifested by aciduria (pH < 5.5), glycosuria, aminoaciduria, phosphaturia and hypokalemia (Fanconi's syndrome). This is due to renal defect in HCO_3^- reclamation in face of acidosis. With serum HCO_3^- limited between 15 mEq/L and 18 mEq/L, acidosis is non-progressive. $NaHCO_3$ therapy may enhance renal potassium wasting. Multiple myeloma and chemotherapy with ifosfamide are common causes of acquired proximal (type 2) RTA (Table 4).

Type 3 RTA infantile variant type of type 1and is not used in adult classification.

Table 4: Disorders associated with renal tubular acidosis.

Renal defect in net acid excretion, classic distal renal tubular acidosis (RTA 1)	*Renal defect in HCO_3^- reclamation, proximal renal tubular acidosis (RTA 2)*
• *Systemic or tubulointerstitial disease* – Cirrhosis – Medullary sponge kidney – Cryoglobulinemia – Nephrocalcinosis – Chronic pyelonephritis – HIV nephropathy – Renal transplant rejection – Thyroiditis – Hyperparathyroidism – Obstructive uropathy (↑ K+) *Drug or toxin Induced* – Ifosfamide – Amphotericin B – Toluene – Mercury – Classic analgesic nephropathy	• *Selective (Non-Fanconi syndrome)* *Idiopathic*: – Carbonic anhydrase deficiency or inhibition – Drugs: acetazolamide • *Generalized (with Fanconi syndrome)* – *Primary*: Inherited or sporadic – Genetic – Multiple myeloma – Monoclonal gammopathy – Secondary hyperparathyroidism, chronic low Ca, Vit D deficiency, resistance,dependency • *Drugs or toxins*: ▪ Ifosfamide, lead, mercury ▪ *Tubulointerstitial diseases:* ▪ Sjögren syndrome ▪ Medullary cystic disease ▪ Renal transplantation
Generalized Defect of the Distal Nephron with Hyperkalemia (RTA 4)	
• *Mineralocorticoid deficiency*: – Primary aldosterone deficiency: ▪ Adrenal hemorrhage, destruction, infarct ▪ Heparin (LMWH or unfractionated) ▪ Persistent hypotension in RAS modulating drugs (ACEI, ARB) – *Secondary aldosterone deficiency* (hyporeninemic hypoaldosteronism): ▪ Diabetic nephropathy ▪ HIV disease ▪ Tubulointerstitial nephropathy ▪ NSAIDs use	• *Renal tubular dysfunction (Voltage Defect)*: – Drugs interfering with Na channel or Na+/K+-ATPase: ▪ Amiloride, pentamidine, triamterene, trimethoprim, cyclosporine, tacrolimus – *Disorders with tubulointerstitial disease*: ▪ Renal failure ▪ Lupus nephritis ▪ Obstructive uropathy ▪ Renal transplant rejection ▪ Sickle cell disease

(HIV: Human immunodeficiency virus; LMWH: Low-molecular weight heparin; RAS: Renin angiotensin system; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; NSAIDs: Nonsteroidal anti-inflammatory drugs).

by mansdocs.com

Type 4 RTA differs from the former two types in hyperchloremic acidosis coexisting with hyperkalemia, with the later being disproportionate to renal dysfunction. With progressive reduction of glomerular filtration rate (GFR) in advancing renal disease, the acidosis changes its character from one of hyperchloremic to that of high AG and is usually normokalemic till a late stage. Ratio of urine to serum potassium compared to the ratio of urine to serum osmolarity is called transtubular K^+ gradient (TTKG). It is low (< 8) in hyperkalemia of renal origin and high in non-renal origin. Hyperkalemia can independently contribute to metabolic acidosis by interfering with ammonia production in the kidney.

Hyperchloremic metabolic acidosis can also result from rapid increase in extracellular fluid volume (ECF). Excess of cationic amino acids of total parenteral nutrition (TPN) can also result in this condition. Dilution of HCO_3^- caused by excess amount of NaCl administration also leads to this type of acidosis. Utilization of solutions with low chloride content can limit this problem in ICU patients.

RESPIRATORY ACIDOSIS

Primary high CO_2 accumulation in blood due to any etiology causes drop in pH and leads to respiratory acidosis. Untreated, it ends in respiratory depression and eventual respiratory arrest and hypoxia leading to cardiac arrest. If needed, this should be avoided by etiological therapy, oxygen supplementation and ventilation (NIV or invasive). Metabolic compensation to acute respiratory acidosis will be exhibited by appropriate drop in HCO_3^- while maintaining standard base excess (SBE) within normal limits. Failure to do so points out to coexisting metabolic disorder. It can be assessed by:

$$HCO_3^- = [(PaCO_2 - 40)/10] + 24$$ (*see* Table 1).

In chronic respiratory acidosis, both SBE and HCO_3^- are altered and can be assessed by:

$$SBE = 0.4 \times (PaCO_2 - 40)$$
$$HCO_3^- = [(PaCO_2 - 40)/3] + 24$$

Causes of respiratory acidosis include neuromuscular disorders, narcotic drugs, pulmonary embolism, dynamic hyperinflation, alveolar hypoventilation due to acute or chronic lung disease, excess CO_2 insufflations and inappropriate $NaHCO_3$ therapy. Treatment of chronic respiratory acidosis should be targeted towards returning $PaCO_2$ to patient's baseline, not normal $PaCO_2$. Control of fever and carbohydrate excess will also assist in achieving this goal. While ventilating patients with ARDS according to ARDSNet protocol, high $PaCO_2$ levels are permitted (permissive hypercapnea).

Compensatory respiratory acidosis to metabolic alkalosis can be assessed by using formulae in Table 1. It is a slow process and can take up to 5 days time. One expects that $PaCO_2$ will decrease in metabolic acidosis, but failure to do so signifies combined metabolic plus respiratory acidosis, which is not uncommon in ICU patients.

HIGH ARTERIAL BLOOD pH

RESPIRATORY ALKALOSIS

Primary low $PaCO_2$ leading to high pH is referred to as respiratory alkalosis. Tachypnea leading to low $PaCO_2$ is always an abnormal sign in critical care patient and should not be ignored. Lightheadedness, tetany and convulsions followed by unconsciousness will be later sequence of events.

$PaCO_2$ also decreases in metabolic acidosis as a compensatory response, the integrity of which can be assessed by formulae given above (*see* Table 1). Metabolic compensation to respiratory alkalosis is a slow process taking up to 5 days time. In acute respiratory alkalosis, SBE will be within normal range but HCO_3^- will vary and can be determined by:

$$HCO_3^- = [(40 - PaCO_2)/5] + 24$$

In chronic respiratory alkalosis, both SBE and HCO_3^- will be altered and can be determined as below:

$$SBE = 0.4 \times (PaCO_2 - 40)$$
$$HCO_3^- = [(40 - PaCO_2)/2] + 24$$

Physiological and pharmacological stimulants such as anxiety, pain, fear, salicylates, progesterone and amphetamines can cause respiratory center hyperactivity and lead to loss of CO_2. Early cardiac failure and pulmonary embolism, liver failure and sepsis are often seen as pathological causes of respiratory alkalosis. After addressing the etiological factors, the treatment can be initiated to retain CO_2. Anxiolysis, rebreathing and psychological

by mansdocs.com

management will usually achieve this goal. All CNS depressants should be avoided. In severe cases, electrolyte estimation and correction is important and may be life saving. Very severe uncontrolled tachypnea may necessitate sedation, paralysis and artificial ventilation.

METABOLIC ALKALOSIS

Metabolic alkalosis exhibits high pH accompanied by compensatory respiratory acidosis as evidenced by raised $PaCO_2$, often associated with low potassium and chloride levels. Compensation can be assessed by the formula of 0.75 rise in $PaCO_2$ /1 mEq rise of HCO_3^- (*see* Table 1). The immediate differential diagnosis of this state of high HCO_3^- is chronic respiratory acidosis where pH is low. In ICU patients with mixed disorders, metabolic alkalosis may coexist with other metabolic and respiratory acid-base disorders. To identify these mixed disorders, the (Δ/Δ) ratio of ΔAG (patient's AG – 10) is compared to ΔHCO_3^- (25– patient's HCO_3^-) has to be calculated. When this Δ/Δ ratio is more than 1, i.e. bicarbonate fall is not proportionate to AG rise, there is a mixed metabolic alkalosis plus high AG metabolic acidosis. This can happen when acid loss due to vomiting coexists with uremic acidosis or ketoacidosis. Combined metabolic and respiratory alkalosis with very high pH carries very high mortality.

Metabolic alkalosis primarily presents with symptoms associated with hypovolemia and CNS dysfunction such as confusion, drowsiness with low threshold for seizures, paresthesias, cramps and tetany (which may be masked in ICU patients). Arrhythmias due to hypokalemia and features of low PO_4 will be evident.

Loss of acid H^+, as happens in vomiting or excess nasogastric (NG) aspirate, generates metabolic alkalosis (*generative stage*). Theoretically this can also happen by alkali gain, which is unusual. Under physiological conditions, kidneys can excrete excess HCO_3^-, but when they fail to do so, alkalosis is maintained (*maintenance stage*). This may happen either when there is chloride deficiency or hypokalemia as seen in contraction of ECF volume, even though total body HCO_3^- is normal. Occurrence hypochloremia and hypokalemia together stimulate H^+ ion secretion in collecting ducts through hyperaldosteronism. This kind of alkalosis responds to sodium chloride and K^+ administration. The other kind of alkalosis evolves when there is autonomous or primary hyperaldosteronism, which does not respond to increasing ECF volume through saline (chloride).

Evolution of metabolic alkalosis can also be explained by increase in SID. Severe water depletion leads to parallel increase in Na^+ and Cl^-. Since Na^+ con centration becomes more than Cl^-, a SID develops. Cl^- is lost from GIT or urine in excess to Na^+, and Na^+ is administered in excess to Cl^-. Due to severe deficiency of intracellular cations such as Mg^{2+} and K^+, a transcellular Cl^- deficiency develops and leads to hypochloremic alkalosis.

A large group of metabolic alkalosis patients have contracted ECF, hypokalemia and secondary hyperreninemic hyperaldosteronism with normotension (Table 5). Primary among them are upper GI losses due to vomiting and NG aspirate, which needs to be corrected. Diuretic usage, both thiazides and loop, results in chloride loss in urine without HCO_3^- loss and result in reduced ECF volume, leading to contraction alkalosis, which can be normalized by isotonic saline (Table 6). Proton pump inhibitor (PPI) administration and diuretic stoppage will be beneficial. Bartter's syndrome (classic and antenatal types) and Gitelman syndrome (in children) are autosomal recessive disorders due to impaired Cl^- absorption. Na^+ and K^+ supplementation along with magnesium is the treatment and NSAIDs may help by suppressing renin production. Mg^{2+} and K^+ deficiency can cause mild metabolic alkalosis. If both salt and K^+ are restricted, this becomes severe and will respond only to K^+ supplementation.

METABOLIC ALKALOSIS—STEPWISE DIAGNOSIS (FLOWCHART 2)

Causes of metabolic alkalosis can be analyzed by assessment of Extracellular volume (ECV) status status (orthostasis), blood pressure, serum K^+, renin-aldosterone system and urine electrolytes, mainly Cl^+ (*see* Table 5). In prolonged vomiting or alkali intake, urine is relatively alkaline with elevated urine Na^+ and K^+ but low Cl^-. Relative acidic urine and low concentration of all three ions in urine point towards prior vomiting, prior diuretic intake or post-hypercarbic state. If the ionic concentrations in acidic urine are not low, then Mg^{2+} deficiency or current diuretic intake are likely. High urine Cl^- and hypertension denote hyperaldosteronism.

Critically sick patients are prone to have deficient renal function and thus will be unable to excrete extra load of alkali such as extraneous $NaHCO_3$, acetate or citrate load (transfusions or CRRT), TPN and anion exchange resins. Prolonged hypercapneic patients develop metabolic

by mansdocs.com

Table 5: Common causes of metabolic alkalosis.

- *Exogenous HCO_3^- Loads*
  - Acute alkali administration
  - Milk-alkali syndrome
  - Massive blood transfusion
- Effective ECF contraction, normotension, hypokalemia and secondary hyperreninemic hyperaldosteronism
  - *Gastrointestinal origin*:
    - Vomiting and NG aspiration
    - Chloride loosing diarrhea
  - *Renal origin*:
    - Thrazides and loop diuretics
    - Edematous states
    - Mineralocorticoid excess
    - Post-hypercemia-hypoparathyroidism
    - Recovering lactic acidosis and DKA
    - Mg^{++} deficiency and K^+ depletion
    - Carbohydrate refeeding
    - Bartter's Gitelman's syndromes
- *ECF volume expansion, Hypertension, K^+ Deficiency and hypermineralocorticoidism*
  - *High Renin*:
    - Renal artery stenosis
    - Accelerated hypertension
    - Renin-secreting tumor
    - Estrogen therapy
  - *Low Renin*:
    - Primary aldosteronism
    - Adenoma
    - Hyperplasia
    - Carcinoma
    - Glucocorticoid suppressible
  - *Adrenal enzymatic defects*:
    - 17μ or 11β-Hydroxylase deficiency
  - *Cushing's syndrome or disease*:
    - Ectopic ACTH
    - Adrenal carcinoma or adenoma
    - Primary pituitary
- Gain-of-function mutation of ENaC with ECF expansion, hypertension, K^+ deficiency and hyporeninemic hypoaldosteronism
  - Liddle's syndrome

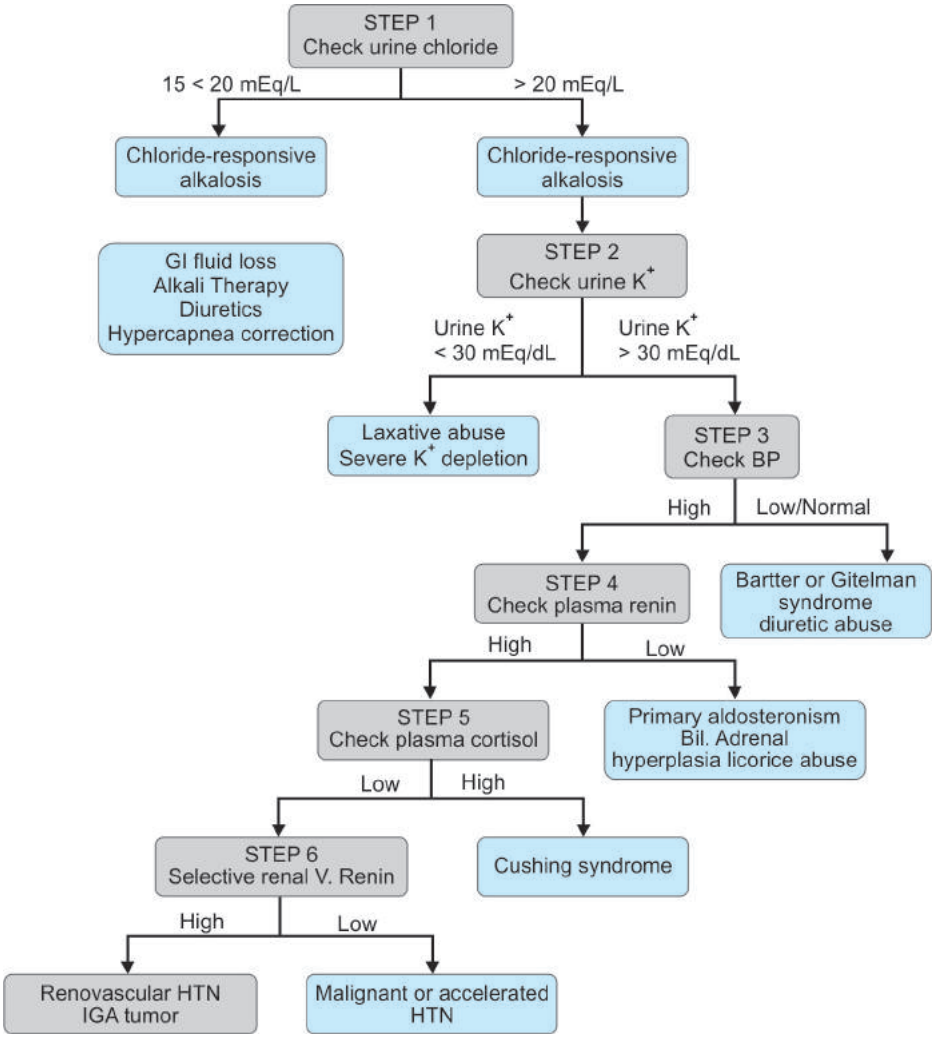
(ECF: Extracellular fluid; NG: Nasogastric; DKA: Diabetic ketoacidosis; ACTH: Adrenocorticotrophic hormone).

Table 6: Classification of metabolic alkalosis.

Saline (CT) responsive alkalosis	*Saline (CT) unresponsive alkalosis*
• Low urinary chloride	• High or normal urinary chloride
– Normotensive	– Hypertensive
▪ Vomiting, Nasogastric aspiration	▪ Primary aldosteronism
▪ Post-diuretic usage	▪ Cushing's syndrome
▪ Post-hypercapnia	▪ Renal artery stenosis
▪ $NaHCO_3$ loading	▪ Renal failure plus alkali therapy
▪ K^+ deficiency	– Normotensive
– Hypertensive	▪ Mg^{++} deficiency
▪ Liddle's syndrome	▪ Severe hypokalemia
	▪ Bartter's syndrome
	▪ Gitelman's syndrome
	▪ Diuretics (ongoing use)

by mansdocs.com

Flowchart 2: Metabolic alkalosis—stepwise diagnosis.



Source: Adopted and modified from DuBose TD Jr. Acid-base disorders. In: Brenner BM. Brenner and Rector's the Kidney, 8th edition. Philadelphia: Saunders; 2008
(HTN: Hypertension).

acidosis after correction of high CO_2, after artificial ventilation. Though HCO_3^- is high in this condition, the contracted ECF has to be corrected with Cl^- containing solutions. Metabolic alkalosis may also develop during post-therapeutic stage of lactic acidosis and DKA.

Various mild and slow metabolic alkalosis syndromes which present with hypervolemia, hypertension and hyperaldosteronism (*see* Table 5), may be primary or secondary. Primary aldosteronism warrants correction, if needed by surgery or administering an aldosterone blocker like amiloride. Spiranolactone can be used for bilateral adrenal hyperplasia. Patients with CHF and advanced liver disease with renal dysfunction may not tolerate ECF volume expansion. Acetazolamide may benefit these patients by promoting renal loss of HCO_3^-, but cautious monitoring of serum K^+ levels are advised. Pertinent to ICU patients is the frequent and excess usage of steroids.

Intravenous administration of dilute isotonic HCl or oral NH_4Cl may be effective. Ultimately, low HCO_3^- and high Cl^- hemodialysis is used if renal function is impaired.

With increasing complexity of medical diagnosis and management and new biochemical tools of identification of metabolic problems, it has become more essential to

by mansdocs.com

understand the physiology and etiopathology of acid-base imbalances of critically sick patients. Clear understanding of subset of these syndromes leads to precise management and gives sooner and better outcome in these patients.

BIBLIOGRAPHY

1. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders, Second of two parts. N Engl J Med. 1998;338(2):107-11.
2. Black RM. Metabolic acidosis and metabolic alkalosis. In: Irwine RS, Rippe JM (Eds). Intensive Care Medicine, 7th edition. New Delhi: Lippincott Williams & Wilkins; 2012. pp. 831-42.
3. Dubose TD, Daeihagh P. Metabolic acidosis and alkalosis. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP (Eds). Textbook of Critical Care, 6th edition. Philadelphia: Elsevier Saunders; 2011. pp. 823-40.
4. Venkatraman R, Pinsky M. Patient-centered Acute Care Training (PACT) module. Electrolytes and homeostasis. European Society of Intensive Care Medicine; 2011.

by mansdocs.com

CHAPTER

34

Disorders of Potassium

Yogendra Pratap Singh, Sanjay Kumar Nihlani, Rahul Kumar Anand

A potassium disorder is the most common electrolyte abnormality in hospitalized patients. Of the two conditions, hypokalemia is more common, affecting more patients, while hyperkalemia is potentially more serious and occurs almost exclusively in patients with some underlying renal problem.

PATHOPHYSIOLOGY OF POTASSIUM

The total body potassium content is approximately 50 mEq/kg and is distributed asymmetrically in the body. About 98% is intracellular and only 2%, or 65–70 mEq, is extracellular. In this extracellular component, about 15 mEq or 0.4% of the total body potassium is measurable in the plasma. This tiny fraction of total body potassium is maintained in a fairly narrow serum concentration of 3.5–5.0 mmol/L. In comparison to the extracellular compartment, the intracellular potassium concentration is about 150 mmol/L. Na^+/K^+-ATPase enzyme pump, located in the cell membrane, maintains the potassium concentration gradient by actively transporting potassium into and sodium out of the cells.

HYPOKALEMIA

Hypokalemia is defined as serum potassium concentration less than 3.5 mEq/L. The causes of hypokalemia fall in three main categories: decreased potassium intake, transcellular shift of potassium from extracellular to intracellular compartments, or increased potassium losses. The most common cause is increased losses from renal or gastrointestinal tract.

Causes of Hypokalemia

- *Decreased potassium intake*: It alone rarely causes hypokalemia, but it can increase the severity of other causes of potassium depletion such as diuretics. The minimum daily dietary requirement for potassium is 40–50 mEq/day.
- *Transcellular potassium shifts* movement of potassium from extracellular compartment into cells relatively uncommon cause of clinically significant hypokalemia. It occurs with increased availability of insulin, elevated β-adrenergic activity, metabolic and respiratory alkalosis, hypokalemic periodic paralysis and hypothermia.
  - *Metabolic and respiratory alkalosis* both can contribute to hypokalemia due to exchange of extracellular potassium for intracellular hydrogen ions.
  - *Increased availability of insulin*: Insulin promotes the entry of potassium into skeletal muscle and hepatic cells by increasing activity of Na^+/K^+-ATPase pump in the cell membrane. This effect is most prominent after giving insulin to diabetic ketoacidosis patients.
  - *Elevated β-adrenergic activity*: Catecholamines via β2-adrenergic receptors promote potassium entry into cells by increasing Na^+/K^+-ATPase activity. Administration of β-adrenergic agonist such as salbutamol, terbutaline or epinephrine may decrease plasma potassium concentration by 0.5–1.0 mEq/L. Transient hypokalemia can occur with stress-induced release of epinephrine as in

by mansdocs.com

acute illness, coronary ischemia theophylline intoxication or alcohol withdrawal.
  - *Hypokalemic periodic paralysis* is a rare disorder of uncertain cause characterized by potentially fatal episodes of muscle weakness or paralysis.
- *Excessive loss of potassium*: The most common cause of hypokalemia is the excessive loss of potassium, either in the stool or via urine.
  - *Gastrointestinal losses*: Potassium losses via the gastrointestinal tract are likely the second most common cause of hypokalemia, and results primarily from losses in the stool.
  - *Normally, only about 10% of total potassium excretion (~10 mEq) each day* is via stool. Any cause of increased stool volumes will increase the amount of potassium loss and can result in hypokalemia if the intake of potassium is not increased. Vomiting and nasogastric suctioning by themselves do not cause significant potassium loss as the normal gastric fluid only contains 5–10 mEq/L.
  - *Renal losses*: Hypokalemia due to increased potassium loss in the urine is probably the most common cause of hypokalemia.
  - *Potassium losses due to increased urinary flow or delivery of sodium to distal nephron*: Diuretics are the most common drug-related cause of hypokalemia. Ethacrynic acid and loop diuretics both increase sodium and chloride delivery to the distal collecting duct, which results in increased potassium secretion and chloride depletion.
  - Osmotic diuresis from poorly controlled diabetes mellitus or the use of mannitol or saline diuresis to treat hypercalcemia may also cause increased renal potassium loss. Administration of high doses of some antibiotics, such as penicillin or its derivatives, increases potassium secretion.
  - Rare causes of hypokalemia due to increased distal sodium delivery include type I and type II renal tubular acidosis (RTA), Gitelman syndrome, and Bartter syndrome. RTA is one of the few disorders in which hypokalemia and metabolic acidosis occur.
  - *Increased mineralocorticoid activity*: Aldosterone is the primary hormonal regulator of renal potassium secretion. Increased aldosterone levels leads to increased potassium secretion into the urine. Secondary hyperaldosteronism is the outcome of the normal response to a variety of disease states causing decreased intravascular volume and decreased renal perfusion. Both result in increased potassium wasting by the kidneys.
  - *Other renal etiologies of potassium loss*: Hypomagnesemia frequently occurs in many patients who are also at risk for hypokalemia (e.g. patients with congestive heart failure and on diuretics, alcoholics). Hypomagnesemia promotes potassium excretion; a direct effect of magnesium on tubular potassium transport is likely.

Table 1: Organ system effects of hypokalemia.

Cardiac	• Dysrhythmias • Conduction defects • Increased likelihood of dysrhythmias due to digitalis
Skeletal muscle	• Weakness • Paralysis • Rhabdomyolysis • Fasciculations and tetany
Gastrointestinal	• Ileus
Renal	• Nephrogenic diabetes insipidus • Metabolic alkalosis

Clinical Manifestations of Hypokalemia

The signs and symptoms of hypokalemia are primarily related to changes in the ratio of extracellular to intracellular potassium, and its impact on the resting electrical potential across cell membranes. The organ systems primarily affected by hypokalemia are: cardiac, skeletal muscle, gastrointestinal and renal. The majority of hypokalemic patients have serum potassium levels of 3.0–3.5 mEq/L and are asymptomatic. Moderately hypokalemic patients (serum potassium levels of 3.0–2.5 mEq/L) may demonstrate significant proximal muscle weakness (Table 1).

Severely hypokalemic patients (serum potassium levels below 2.5 mEq/L) may develop rhabdomyolysis, myoglobinuria, an ascending symmetric paralysis with a clear sensorium and even respiratory arrest.

Electrocardiographic changes may be present (Table 2 and Fig. 1). Patients without heart disease rarely demonstrate any significant cardiac abnormalities due to hypokalemia. Numerous studies have demonstrated an increased incidence of ventricular dysrhythmias in patients with underlying heart disease.

by mansdocs.com

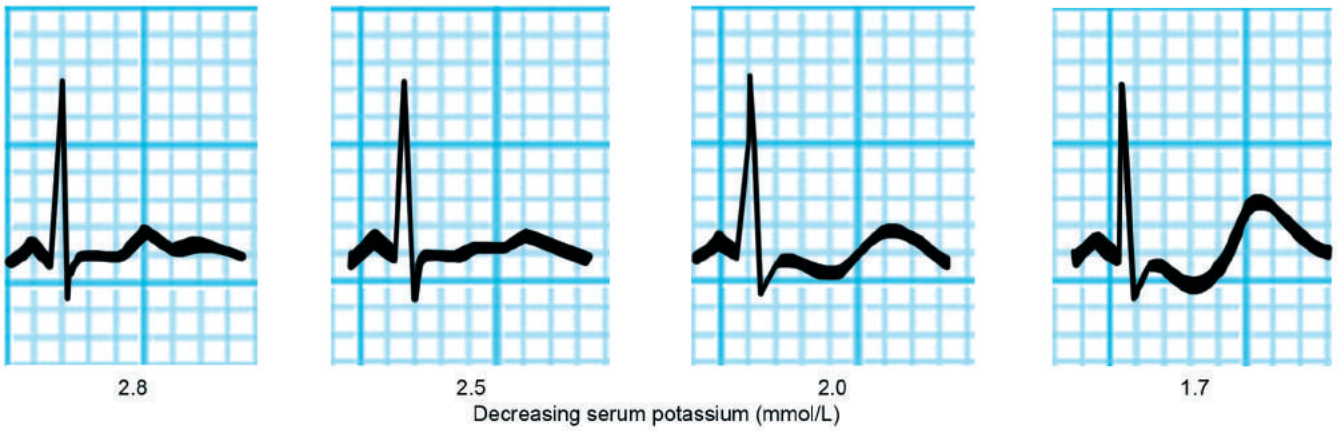


Fig. 1: Electrocardiographic changes associated with hypokalemia.

Table 2: Electrocardiographic changes associated with hypokalemia.

• Apparent QT interval prolongation
• Reduction in T wave amplitude
• T wave inversion
• Appearance of U waves

Hypokalemia has a number of effects on renal function. Patient's may present with symptoms of polyuria and polydipsia due to impaired ability to concentrate the urine and a resulting picture of nephrogenic diabetes insipidus.

Diagnosis of Hypokalemia

In most cases, a thorough history and physical examination reveal the cause (e.g. severe diarrhea, use of diuretics without potassium supplementation). If the etiology is still unclear, measurement of urinary potassium excretion, is helpful. A 24-hour urinary potassium is more than 20 mEq/L in renal losses, and less than 20 mEq/L in extrarenal losses.

Treatment of Hypokalemia

Optimal therapy depends on the severity of the potassium deficit. Strategies aimed at achieving and maintaining normokalemia must take into account such factors as: (1) the presence of underlying medical conditions (e.g. congestive heart failure, coronary artery disease), (2) the use of medications that alter potassium levels (e.g. non-potassium-sparing diuretics) or that lead to arrhythmias in the presence of hypokalemia (e.g. cardiac glycosides).

Potassium Deficit

In general, the loss of 200–400 mEq of potassium is required to lower the plasma potassium concentration from 4 mEq/L to 3 mEq/L.

Potassium Preparations

Intravenous or oral potassium chloride is generally the preferred treatment for hypokalemia. Use of the chloride salt has two important advantages. First, potassium chloride more rapidly raises the plasma potassium concentration than does potassium bicarbonate or potassium citrate. Second, most patients with hypokalemia also have metabolic alkalosis. Potassium must be given with chloride to such patients if both the hypokalemia and the alkalosis are to be corrected optimally. In comparison, potassium bicarbonate or potassium citrate can be given to patients with hypokalemia and metabolic acidosis such as occurs in RTA and chronic diarrheal states.

Merely increasing the intake of potassium-rich foods, such as oranges and bananas, are generally less effective in the absence of renal insufficiency. These foods contain phosphate and citrate rather than chloride and are, therefore, less likely to correct the hypokalemia and metabolic alkalosis.

Potassium chloride can be given intravenously to patients who are unable to eat or who have severe hypokalemia. A saline solution is preferred to a dextrose solution for initial therapy.

Mild-to-Moderate Potassium Depletion

The majority of patients have a plasma potassium concentration between 3.0 mEq/L and 3.5 mEq/L; this degree

by mansdocs.com

of potassium depletion usually produces no symptoms, except in patients with advanced liver disease or in patients with heart disease, particularly if they are taking digoxin. Treatment in this setting is directed toward replacing the lost potassium, usually beginning with 40–80 mEq of potassium chloride per day, and toward treating the disorder responsible for the loss of potassium.

Severe Hypokalemia

Potassium repletion is more urgent for patients with profound or symptomatic hypokalemia (i.e. arrhythmias, marked muscle weakness), if serum potassium is less than 2.5 mEq/L or less than 3 mEq/L in patient.

Receiving digoxin or if symptoms are present is replaced potassium intravenously. There are two potential limitations to intravenous therapy: a maximum concentration of 50–60 mEq/L can be administered via a peripheral vein without irritation. Faster intravenous replacement requires a central venous catheter. In general, the maximum rate of intravenous potassium administration is 10–20 mEq/hour, although as much as 20–30 mEq/hour has been given to selected patients with life-threatening arrhythmias. Potassium administration must be titrated against periodic rechecking of the serum levels.

HYPERKALEMIA

Hyperkalemia is defined as potassium level more than 5.5 mEq/L, some authorities further divides hyperkalemia into:

- *Mild*: 5.5–6.5 mEq/L with only minor electrocardiographic changes
- *Moderate*: 6.6–8.0 mEq/L with electrocardiographic changes limited to peaking of T waves
- *Severe*: More than 8.0 mEq/L or any level with a widened QRS complex, atrioventricular block or ventricular dysrhythmias.

Etiology

There are three main mechanisms of hyperkalemia:

1. Reduced glomerular rate
2. Effective hypoaldosteronism
3. Transcellular shift.

The most common cause of increased serum potassium concentration is probably pseudohyperkalemia caused by hemolysis of red blood cells in the blood sample. Normal kidneys eventually excrete potassium loads, so sustained nonartifactual hyperkalemia usually implies diminished renal potassium excretion. However, other factors usually contribute.

Causes of Hyperkalemia

Pseudohyperkalemia

- Hemolysis
- Distal to tourniquet or with fist clenching
- Marked leukocytosis (white blood cell count > 50,000 mm^3)
- Marked thrombocytosis (platelets >1 million mm^3).

Decreased Potassium Elimination

- Acute or chronic decreased glomerular filtration rate (5–10 mL/minute)
  - Acute or chronic renal failure
- Hypoaldosteronism
  - With low renin levels (hyporeninemic hypoaldosteronism)
    - Elderly
    - Diabetic
    - Interstitial nephritis
    - Obstructive uropathy
    - Systemic lupus erythematosus
    - Amyloidosis
    - Acquired immunodeficiency syndrome
    - Nonsteroidal anti-inflammatory drugs.
  - With high renin levels (hyporeninemic hypoaldosteronism)
    - Addison's disease
    - Angiotensin-converting enzyme inhibitors
    - Angiotensin receptor blockers
    - Heparin.
- End-organ resistance to aldosterone (normal or elevated aldosterone)
  - Systemic lupus erythematosus
  - Sickle cell anemia
  - Obstructive uropathy
  - Transplantation
  - Potassium-sparing diuretic spironolactone.
- Sodium channel blockade
  - Potassium-sparing diuretics amiloride, triamterene
  - Trimethoprim (blocks sodium reabsorption)
  - Pentamidine (blocks sodium reabsorption).
- Increased potassium load
  - Potassium supplements

by mansdocs.com

  - Dietary salt substitutes
  - Potassium penicillin
  - Massive blood transfusion
  - Poisoning, e.g. potassium chloride water softener pellet ingestion.
- Transcellular shifting
  - Insulin deficiency
  - Rhabdomyolysis/increased tissue catabolism
  - Acidosis
  - Hypertonicity
  - Exercise
  - Hyperkalemic periodic paralysis
  - Drugs
    - Nonselective β-blockers (inhibits Na^+/K^+-ATPase pump)
    - Digitalis toxicity (inhibits Na^+/K^+-ATPase pump)
    - Succinylcholine (membrane leakage).

The level at which treatment should be initiated has not been established by evidence. According to recent reviews, it is recommended to start nonpharmacological steps at levels above 5.5 mEq/L, and pharmacologic interventions should be initiated at level of 6 mEq/L or greater. However, manifestations of hyperkalemia depend firstly upon serum K^+ level as well as the rate of rise in K^+ levels. Secondarily, concurrent metabolic disturbances may ameliorate (e.g. hypernatremia, hypercalcemia, alkalemia) or exacerbate (e.g. hyponatremia, hypocalcemia, acidemia) the electrophysiologic consequences of hyperkalemia.

Clinical Manifestations of Hyperkalemia

Hyperkalemia have a variety of adverse clinical consequences, which may be magnified in the critically ill patients. The most serious of these manifestations occur in excitable tissues.

Cardiac Effects

Hyperkalemia depolarizes the cell membrane, slows ventricular conduction, and decreases the duration of the action potential. These changes produce classic electrocardiographic manifestations of hyperkalemia including; peaked T waves, widening of the QRS complex, loss of the P wave, "sine wave" configuration, or ventricular fibrillation and asystole. The sensitivity of the electrocardiogram to reveal changes of hyperkalemia is quite low. However, it increases in proportion to the severity of the hyperkalemia, but normal electrocardiograms have been observed even with extreme hyperkalemia and the first cardiac manifestation of hyperkalemia may be ventricular fibrillation. Given this insensitivity of the electrocardiogram, electrocardiographic changes should not be considered necessary for the emergency treatment of severe hyperkalemia.

Neuromuscular Effects

Hyperkalemia may cause paraesthesias and weakness, which may progress to a flaccid paralysis with typical sparing the diaphragm. Deep tendon reflexes are depressed or absent. Cranial nerves are rarely involved and sensory changes are minimal.

Metabolic Effects

Hyperkalemia decreases renal ammoniagenesis, which by itself may produce a mild hyperchloremic metabolic acidosis, and this will limit the kidney's ability to excrete an acid load and, thus, prevents correction of a metabolic acidosis.

Treatment of Severe Hyperkalemia

In general, the initial treatment of severe hyperkalemia is independent of the cause of the disturbance, whereas the management of chronic hyperkalemia depends on an understanding of its pathogenesis. Therapy of acute or severe hyperkalemia is directed at preventing or ameliorating its untoward electrophysiologic effects on the myocardium. The goals of therapy, in chronological order, are as follows (Table 3):

- Antagonize the effect of potassium on excitable cell membranes
- Redistribute extracellular potassium into cells
- Enhance elimination of potassium from the body.

Membrane Antagonism

Calcium: Calcium is used to temporarily antagonize and stabilize the cardiac membrane in patients with significant ECG abnormalities and when it is potentially dangerous to wait 30–60 minutes for other therapies to take effect. Calcium is beneficial even in patients who are normocalcemic. Calcium gluconate is generally used. The calcium dose can be repeated in 10 minutes. Calcium chloride can also be used with 10 mL of a 10% solution providing three times the elemental calcium than that of 10 mL of 10% calcium gluconate. This higher dose of calcium, theoretically, may be beneficial in patients with

by mansdocs.com

Table 3: Emergency treatment of hyperkalemia.

Agent	*Dose*	*Onset*	*Duration*	*Complications*
Membrane stabilization				
Calcium gluconate (10%)	10 mL IV over 10 minutes	Immediate	30–60 minutes	Hypercalcemia
Hypertonic (3%) sodium chloride	50 mL IV push	Immediate	Unknown	Volume overload hypertonicity
Redistribution				
Insulin (short acting)	10 units IV push, with 25–40 g dextrose (50% solution)	20 minutes	4–6 hours	Hypoglycemia
Albuterol	20 mg in 4 mL normal saline solution, nebulized over 10 minutes	30 minutes	2 hours	Tachycardia inconsistent response
Elimination				
Loop diuretics				
Furosemide	40–80 mg IV	15 minutes	2–3 hours	Volume depletion
Bumetanide	2–4 mg IV			
Sodium bicarbonate	150 m mol/L IV at variable rate	Hours	Duration of infusion	Metabolic alkalosis volume overload
Sodium polystyrene sulfonate (SPS, Kayexalate, Kionex)	15–30 g in 15–30 mL (70% sorbitol orally)	> 2 hours	4–6 hours	Variable efficacy intestinal necrosis
Hemodialysis		Immediate	3 hours	Arrhythmias

marked cardiovascular compromise and instability. Calcium can potentiate digitalis toxicity. There are several case reports of sudden cardiac deaths in patients given intravenous calcium while patient is also receiving digitalis glycosides. If it is necessary to give calcium to a patient taking digitalis, it is recommended that the calcium be added to 100 mL of D5W, and infused over 20–30 minutes.

Hypertonic saline: Intravenous hypertonic sodium chloride has been shown to reverse the electrocardiographic changes of hyperkalemia in patients with concurrent hyponatremia. This effect is mediated by a change in the electrical properties of cardiomyocytes rather than by a reduction in serum K^+. Efficacy of hypertonic saline in eunatremic patients is not well established. Therefore, the use of hypertonic (3%) saline should be restricted to hyponatremic patients with hyperkalemia, with an awareness of the volume overload that may ensue with this.

Intracellular Shifting

Insulin: Insulin reliably and most consistently lowers serum K^+ (even in patients with end-stage renal disease) and is indicated in all cases of hyperkalemia requiring emergency treatment. The effect is mediated by activation of Na^+/K^+-ATPase, apparently by recruitment of intracellular pump components into the plasma membrane. The treatment should lower the potassium level by about 0.5–1.2 mmol/L in 1 hour. If glucose levels are less than 250–300 mg/dL then glucose should also be administered with the insulin to prevent hypoglycemia (typical 50 mL of 50% glucose; 1 ampule or 25 g). Hypoglycemia occurs in 11–75% of normoglycemic patients, in 30–60 minutes, if they are given less than 25 g of glucose. In all patients treated with insulin, close glucose monitoring and if necessary, infusion of 10% dextrose at 50 mL/h or repeat dextrose boluses can be given as needed. Insulin should be used without dextrose in hyperglycemic patients, because hyperkalemia in those patients maybe because of the hyperglycemia itself.

β-adrenergic agonists: Another possible treatment to shift potassium intracellularly is intravenous or nebulized β2 agonists. Intravenous preparation of salbutamol is not available in India. The nebulized dose is 10–20 mg, which is higher than the typical 2.5–10 mg every 1–4 hours recommended for acute bronchospasm. The effect of insulin is additive with that of salbutamol. Approximately 40% patients seem to be resistant to the hypokalemic effect of salbutamol. The mechanism for this resistance is unknown, and there is currently no basis for predicting which patients will respond. For that reason, salbutamol

by mansdocs.com

should never be used as a single agent in the treatment of severe hyperkalemia. Nebulized salbutamol and levosalbutamol were equally effective at lowering serum potassium; however, levosalbutamol achieved a more immediate response upon administration and resulted in fewer adverse effects increased heart rate, tremors, palpitations and mild anxiety.

Bicarbonate: Historically bicarbonate has been suggested as the treatment of hyperkalemia. However, the routine use of sodium bicarbonate is controversial and has fallen out of favor. The routine use of bicarbonate in hyperkalemia is not recommended.

Elimination of Potassium from the Body

Diuretics: Loop diuretics (e.g. furosemide, bumetanide and ethacrynic acid) can be used to increase renal tubular flow and potassium elimination. However, the patient must have an adequately functioning kidney, and this is obviously a limiting factor for patients with chronic renal failure. In other patients, in particular with hyporeninemic hypoaldosteronism, this is an effective additional treatment.

Hemodialysis: It is the most definitive and effective method of rapidly lowering the serum potassium. Serum K^+ falls by over 1 mEq/L in the first 60 minutes of hemodialysis, and a total of 2 mEq/L by 180 minutes, after which it reaches a plateau. Rebound always occurs after dialysis with 35% of the reduction abolished after an hour and nearly 70% after 6 hours; the magnitude of the postrebound serum K^+ is proportional to the predialysis K^+ level. Patient should have continuous ECG monitoring, because of the possibility of serious ventricular arrhythmias, which may precipitate by dialysis.

Exchange resin: Sodium polystyrene sulfonate (Kayexalate) is an exchange resin that works across the gastrointestinal mucosa. This can be given orally or as a retention enema; however, oral route is considered to be more effective because of the longer transit time through the gut. Because of slower onset of action, and serious, albeit infrequent, colonic necrosis, sodium polystyrene sulfonate is a poor choice for the treatment of urgent hyperkalemia.

ADDRESSING UNDERLYING CAUSE

Finally, treating the underlying conditions, changing medications or altering diets may be indicated. If the cause is not apparent, further evaluation for worsening renal function, determining renin and aldosterone levels, checking cortisol levels, calculating the transtubular potassium gradient, and so on, are indicated.

BIBLIOGRAPHY

1. Black MR. Disorders of plasma sodium and plasma potassium. In: Irwin RS, Rippe JM (Eds). Intensive Care Medicine, 7th edition. Philadelphia: Lippincott; 2012. pp 856-66.
2. Cohn JN, Kowey PR, Whelton PK, et al. New guidelines for potassium replacement in clinical practice. Arch Intern Med. 2000;160:2429-36.
3. Timothy JS, Robert WW. Disorders of Potassium. Emerg Med Clin N Am. 2005;23:723-47.
4. Weisberg LS. Management of severe hyperkalemia. Crit Care Med. 2008;36:3246-51.

by mansdocs.com

CHAPTER

35

Sodium Disorders

Yogendra Pratap Singh, Manish Gupta, Akhil Taneja

HYPERNATREMIA

INTRODUCTION

Hypernatremia is defined as a serum sodium (Na^+) concentration exceeding 145 mmol/L. The Edelman equation shows the serum Na^+ concentration as a function of the total exchangeable sodium and potassium in the body and the total body water (TBW).

$$[Na^+] = \frac{(Na^+_{\text{total body}} + K^+_{\text{total body}})}{\text{Total body water}}$$

Increase → Gain of sodium

Decrease → Loss of free water

(While Na^+ total body stands for total exchangeable sodium and K^+ total body stands for total exchangeable potassium).

Consequently, hypernatremia can only develop as a result of either a gain of sodium or a loss of free water or a combination of both. Although hyponatremia can be associated with iso-osmolality or even hyperosmolality when an additional osmotically active particle is present in excess (e.g. glucose in hyperglycemia), hypernatremia is always associated with hyperosmolality. Under normal conditions, thirst is the major defense mechanism against the development of hypernatremia. Osmolality is regulated within narrow ranges in the healthy individual, and even slight elevations in osmolality lead to the development of thirst and the secretion of antidiuretic hormone (ADH). Thus, hypernatremia usually develops only when there is no access to free water, when the person has a disturbed sensation of thirst or when he/she is unconscious. Critically ill patients are often unconscious, intubated, or sedated, and their "water intake" is mainly managed by the physician, making them prone to the development of hypernatremia.

FREQUENCY AND TIMING OF HYPERNATREMIA IN CRITICALLY ILL PATIENTS

Hypernatremia is a much more common finding in critically ill patients treated in intensive care units (ICUs). Upon admission to the ICU, between 2% and 6% of patients are already hypernatremic. Between 6% and 26% of patients in medical intensive care unit (MICU) and 4–10% of patients become hypernatremic during the course of treatment respectively.

WATER HOMEOSTASIS AND PATHOPHYSIOLOGY OF HYPERNATREMIA (FIG. 1)

Sodium is the primary extracellular solute and alterations in body water balance, through net loss or gain of body water can lead to significant changes in plasma Na^+ concentration and tonicity. Therefore, water homeostasis is critical for maintaining Na^+ concentration and hence, tonicity of the plasma within a narrow range for optimal cellular function.

by mansdocs.com

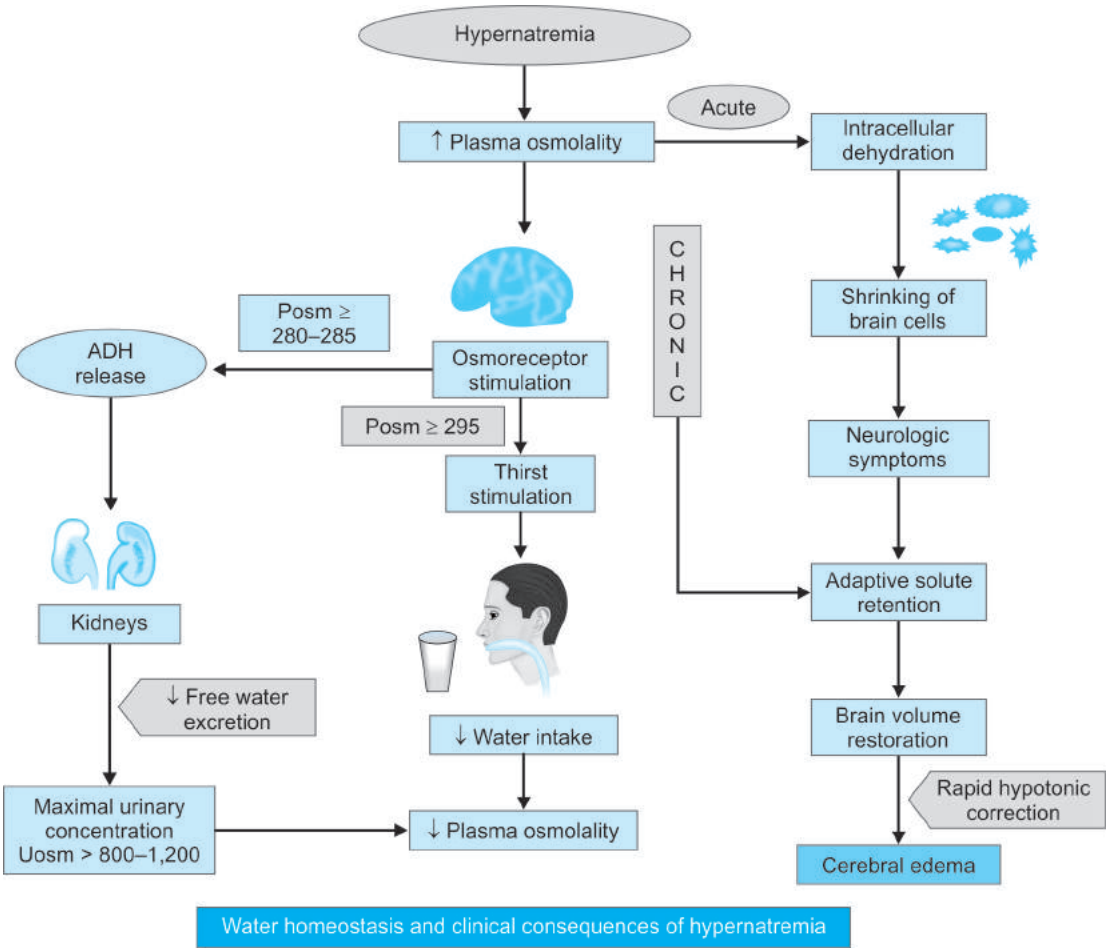


Fig. 1: Water homeostasis is closely regulated in body by control of thirst and ADH release which prevents development of hypernatremia and hyperosmolality.
(ADH: Antidiuretic hormone; Posm: Plasma osmolality; Uosm: Urine osmolality).

Plasma hypertonicity associated with hypernatremia initiates water movement across the cell membrane, leading to considerable intracellular volume loss with variable degree of extracellular volume depletion, depending on alteration in total body sodium content. Extracellular fluid volume depletion is usually proportionate to intracellular volume loss in pure water loss such as in acute diabetes insipidus but may be substantial in conditions with hypotonic fluid losses, as a result of concomitant loss of sodium and ensuing decrease in body sodium content. On the other hand, hypernatremia associated with primary sodium gain may initially expand extracellular fluid volume by drawing intracellular water and induces natriuresis, usually accompanied by water loss and net free water deficit. Plasma Na^+ concentration does not correlate well with body sodium content and total body sodium may be normal, decreased or increased in presence of hypernatremia.

CONSEQUENCES OF HYPERNATREMIA

Hypernatremia and the associated hyperosmolar state have a multitude of effects on bodily functions (Fig. 2). The development of hypernatremia and, therefore, hyperosmolality leads to a shift of free water from the intracellular to the extracellular space. This shift leads to brain cell shrinkage, which can even lead to vascular rupture and permanent neurologic deficits in severe cases. Neuromuscular effects of hypernatremia include muscle weakness or cramps. In infants, hypernatremia has been shown to cause restlessness, lethargy, hyperpnea, and even coma. It has been hypothesized that the neurologic impairment caused

by mansdocs.com

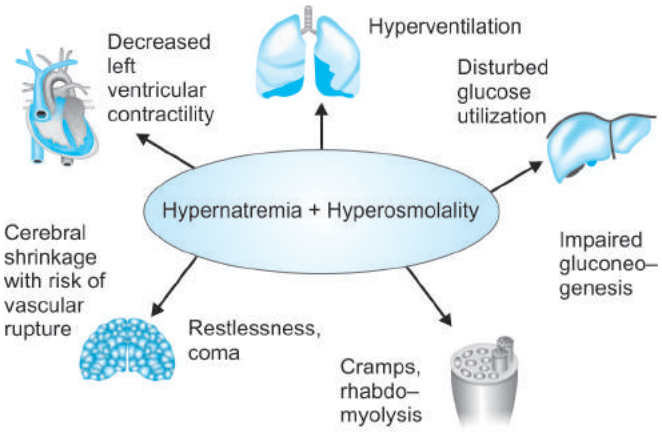


Fig. 2: Consequences of hypernatremia.

by the presence of hypernatremia may even lead to prolonged mechanical ventilation.

In vitro studies have demonstrated that the induction of hyperosmolality leads to an impairment in glucose utilization and glucagon-dependent glucose release. In healthy volunteers, it has been shown that the slight increase in serum osmolality from 280 mOsm/kg to 302 mOsm/kg was associated with the severe impairment of insulin-mediated glucose metabolism, thus potentiallycontributing to the development of hyperglycemia in critically ill patients. Hypernatremia has also been shown to impair hepatic gluconeogenesis and lactate clearance. In patients hospitalized for diabetes mellitus who showed hyperosmolality, an increased risk for venous thromboembolism has been demonstrated. Impairment in cardiac function via a decrease in left ventricular contractility has been reported in hypernatremic patients. In addition, severe hypernatremia has been reported to cause rhabdomyolysis and consequent acute renal failure.

INFLUENCE OF HYPERNATREMIA ON THE OUTCOME OF CRITICALLY ILL PATIENTS

Mortality rates in hypernatremic patients were reported to be dramatically increased as compared with normonatremic controls. However, this increase in mortality was mainly attributed to the severity of the underlying disease in hypernatremic ICU patients. Studies focused on the potential impact of hypernatremia on outcomes in critically ill patients on a medical ICU have shown mortality rates between 30 and 48% for patients with serum sodium levels exceeding 150 mmol/L. Even for patients with only slightly elevated serum sodium levels, mortality was elevated as compared with the normonatremic controls (15% vs 30%).

MECHANISM OF HYPERNATREMIA

To determine the origin of hypernatremia in the ICU, it is crucial to precisely document the daily volume input and output including enteral/parenteral nutrition. In any case of more significant increases or decreases in serum sodium, daily urine electrolyte analysis is indicated. Thorough analysis of the volume state and changes in serum sodium levels should ideally be performed before the development of hyponatremia or hypernatremia. Hypernatremia can only develop through either a loss of free water or a gain of serum sodium. However, in the critical care setting, a combination of the two mechanisms is responsible for most cases of hypernatremia. A third rare mechanism for hypernatremia is seen in transient hypernatremia. This form of hypernatremia occurs after severe exertion, and serum sodium may rise 10–15 mmol/L because of the shifting of free water from the extracellular to the intracellular space.

Hypernatremia with Water and Solute Loss

This condition arises by a negative water balance exceeding a concomitant negative cation balance. The resulting hypovolemia is the most common condition in hospitalized hypernatremic patients. Diminished water intake is a pivotal mechanism of increased P-[Na^+]. Individuals at risk of insufficient drinking often have an altered mental status (critical illness, sedation, neurological impairment) or they are intubated patients, infants or geriatric patients. An enhanced water clearance above salt loss contributes to hypernatremia. Fever is a common contributing factor. A high loss through the skin can result from a high temperature in the environment, from exercise or wounds (for example, burns). Gastrointestinal loss of hypotonic fluid is increased by diarrhea (for example, infection, lactulose). A renal concentrating defect frequently contributes to hypernatremia. Loop diuretics contribute, especially in the critically ill patient. Osmotic diuresis (U Osm >300 mOsm with hypernatremia) can be induced by hyperglycemia. Osmotic urea diuresis is seen with excessive protein nutrition and protein wasting and diagnosed by increased electrolyte-free water excretion. Mannitol also induces osmotic diuresis.

by mansdocs.com

A renal concentrating defect is seen with kidney insufficiency. Rare causes are hypercalcemia and potassium depletion.

Hypernatremia with Pure Water Loss

This condition develops when the water balance is negative and the cation balance is normal. The reduction in extracellular volume (ECV) is far less than with a concomitant salt loss. Diminished water intake is obligatory. Individuals with reduced water intake (infants, old, debilitated patients) will have appropriate, maximally concentrated urine. Patients with a functionally decreased vasopressin response to hypertonicity (central or nephrogenic diabetes insipidus) only develop hypernatremia when water intake is restricted (for example, critical illness). Diabetes insipidus occasionally develops in the critically ill patient (for example, by traumatic brain injury and late-phase septic shock) and Uosm is inappropriately low. In rare situations, the set point for osmolality is directly increased due to cerebral disease resulting in essential hypernatremia and reduced thirst at a given Na^+ concentration. Treatment is restoration of the water deficit. Water loss in central diabetes insipidus can be reduced with desmopressin. Treatment of nephrogenic diabetes insipidus is challenging and may comprise drug evaluation, correction of hypercalcemia or hypokalemia and low-solute diet to decrease urine volume and thiazides.

Hypernatremia with Increased Total Body Solute

Hypernatremia with increased ECV develops when the cation balance is positive, which is frequently observed in ICU-acquired hypernatremia. Increased input of cations is mandatory. This is seen in conjunction with correction of water loss with 0.9% NaCl. Also, correction of hypokalemia with hypertonic potassium-containing solutions (for example, 0.9% NaCl added 40 mmol KCl) may contribute to hypernatremia. Hypernatremia can be induced therapeutically with hypertonic saline to reduce intracranial pressure (ICP) or as a side effect seen with $NaHCO_3$ treatment. In healthy individuals, an increased salt load is excreted in the urine. Natriuresis can be diminished in the critically ill patient with a reduced effective circulating volume and a low glomerular filtration rate. A diagnosis of solute overload is made from the history, water- and cation balances and, if available, weight changes. Treatment consists of creating a negative cation balance by reducing the cation input and increasing the cation output with diuretics or, rarely, dialysis.

TREATMENT

Before the correction of hypernatremia, differentiation should be made as to whether hypernatremia is acute or chronic. The diagnosis of acute hypernatremia should only be made if the rise in serum sodium has a documented onset within the last 48 hours. If this is the case, the rapid correction of hypernatremia (up to 8–12 mmol/L/day) is indicated because compensatory mechanisms such as an uptake of solutes into the brain cells have not yet begun. In the case of chronic hypernatremia, compensatory mechanisms have already begun, and too rapid correction may result in cerebral edema, which can even lead to herniation and death. Therefore, correction rates of 8–10 mmol/L/day must not be exceeded.

Treating Underlying Causes

The cause of decreased water intake and source of renal or nonrenal fluid losses should be identified and addressed to prevent ongoing losses while fluid replacement therapy is instituted. The free water needs of ICU patients unable to report thirst or drink water should be routinely assessed and replaced with appropriate electrolyte-free fluids. Oral intake of water guided by thirst should be encouraged wherever possible. Excessive renal, extrarenal, and insensible losses should be corrected. This may include correction of hyperglycemia and stopping diuretics and osmotic agents such as urea, mannitol, and lactulose. The practice of routinely prescribing isotonic saline or other electrolyte-containing fluids for free water replacement in ICU or hospitalized patients should be discouraged. Hypertonic solution should be used appropriately and risk of hypernatremia from their use recognized. In hypernatremia with free water deficit, can be estimated by using following equation:

Water deficit (L) = 0.6 (0.5 for women) × weight (kg) [(measured Na/normal Na) – 1]

For example, water deficit of a 60 kg man of 160 mmol/L

0.6×60 [(160/140) – 1]

36 [1.14 – 1]

$36 \times 0.14 = 5.04$ L water deficit.

However, frequent measurements of P-[Na^+], P-[K^+] and P-[Glucose] and calculation of [Na^+] corrected are necessary to avoid overcorrection. In severe cases with renal failure, renal replacement therapy should be instituted. Here, the Na^+ content in the replacement fluid/dialysate must be increased to the desired P-[Na^+] by $NaCl^-$ addition to avoid overly rapid correction.

by mansdocs.com

Type of Fluid Replacement

Since hypernatremia basically represents a decrease in TBW relative to sodium content, replacement of free water is the treatment of choice in most cases except when hemodynamic compromise is present. Immediate volume repletion with normal saline is crucial under these circumstances to achieve hemodynamic stability, and free water replacement must be done later to restore normal osmolality. Free water replacement can be given through oral or parenteral routes and oral water intake guided by the thirst is generally preferable in mentally alert patients with mild hypernatremia. Enteral route is also desirable since electrolyte-free water can be given and the risk of hyperglycemia with dextrose containing intravenous fluids can be prevented. However, it may not always be feasible in ICU patients where oral intake is restricted and fluid deficits frequently need to be replenished by intravenous fluid therapy. Any type of hypotonic fluid can be used [0.45% NaCl, 0.3% NaCl, ringers lactate, or 5% dextrose water (D5W)] for correction of hypernatremia, but depending on the fluid [Na^+ + K^+] concentration, more fluid volume and time for correction of hyperosmolality is required for the electrolyte-containing fluids compared to free water or D5W replacement. Sodium-containing hypotonic fluids may be considered in place of electrolyte-free water (D5W) in hypernatremic patients with uncontrolled hyperglycemia or nonketotic hyperosmolar state, as well as in conditions with concomitant loss of sodium and water associated with milder degree of extracellular volume depletion but without hemodynamic instability, where isotonic saline is preferred.

CONCLUSION

Hypernatremia is a common and largely preventable complication of intensive care. It has various adverse physiologic consequences and is associated with poor outcomes. Efforts should focus on the prevention of hypernatremia and adequate correction of the electrolyte disturbance. Management of hypernatremia in critically ill ICU patients may be complicated and following caveats may be valuable:

1. Rate of correction of hypernatremia depends on rapidity and severity of hypernatremia development.
   Note: Na^+ concentration should be measured frequently (6–12 hours), if hypernatremia developed over a period of hours, reducing serum sodium by 1 mmol/L/h is appropriate. In hypernatremia of longer or unknown duration, a slower rate of correction (0.5 mmol/L/h) is recommended. Rapid correction of serum sodium can result in cerebral edema and neurological injury.
2. In presence of hemodynamic instability with hypotension and hypernatremia, intravascular volume should be restored first with isotonic saline prior to free water administration.
3. Daily fluid requirement and any ongoing losses must also be replaced in addition to calculated fluid requirement to achieve desired reduction in plasma sodium levels.
4. Adequate monitoring with serial neurologic examinations and measurements of serum and urine electrolytes every 2–4 hours must be performed during hypotonic fluid therapy.
5. Electrolyte-free water requirements of sick patients not able to maintain adequate oral intake should be routinely estimated and replaced.
6. Oral-free water replacement should be considered in mentally alert patient whenever possible.
7. Free water deficits should be replaced with appropriate electrolyte-free fluids as far as possible and normal saline or other sodium-containing fluids should not be routinely used for replacing all the fluid requirements in critically ill patients.
8. Free water replacement with D5W may cause hyperglycemia in diabetic patients and treatment with insulin or use of alternative fluids should be considered if necessary.
9. Hypernatremia resulting from acute sodium gain is usually iatrogenic and can cause symptoms of volume overload in patients with underlying cardiac or renal compromise.
10. Any underlying causes for hypernatremia should be identified and corrected.

by mansdocs.com

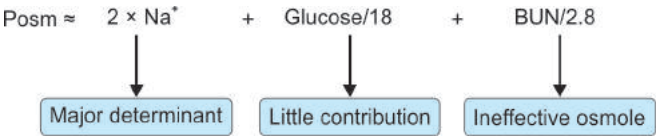
HYPONATREMIA

INTRODUCTION

Hyponatremia is defined as a plasma Na^+ concentration below 135 mEq/L. Hyponatremia represents a disorder of water balance, i.e. relative excess of water rather than deficiency of solute. P-[Na^+] is closely related to plasma osmolality.

Relationship between Plasma Na^+ and Plasma Osmolality

In plasma, Na^+ salts, glucose, and urea [blood urea nitrogen (BUN)] are the major determinants of osmolality. Therefore, the Posm can be estimated by the following formula:



Using this formula, it is evident that the major determinant of the Posm in healthy individuals is the plasma Na^+ concentration.

Because urea can cross almost all cell membranes readily, it cannot promote the movement of water between the intracellular and extracellular spaces. As such, urea is referred to as an ineffective osmole. Glucose normally contributes less than 8 mOsm/kg; the effective Posm correlates best with the p Na^+. Thus, effective Posm can be described as follows:

Posm (effective) ≈ 2 × Na^+

Regulation of P-[Na^+]/Regulation of Plasma Osmolality

P-[Na^+] is tightly regulated between 135 mmol/L and 145 mmol/L primarily by water intake (thirst) and renal water excretion and to a lesser extent by kidney's regulation of cation excretion via the renin-angiotensin-aldosterone system. Thirst is stimulated when P-[Na^+] increases a few percent. It is also stimulated by a decrease in the effective circulating volume, which is the part of the ECV that effectively perfuses the tissue (Fig. 3). Arginine vasopressin (vasopressin or ADH) reduces renal water excretion acting through V_2-receptor in the collecting duct. Vasopressin secretion is stimulated

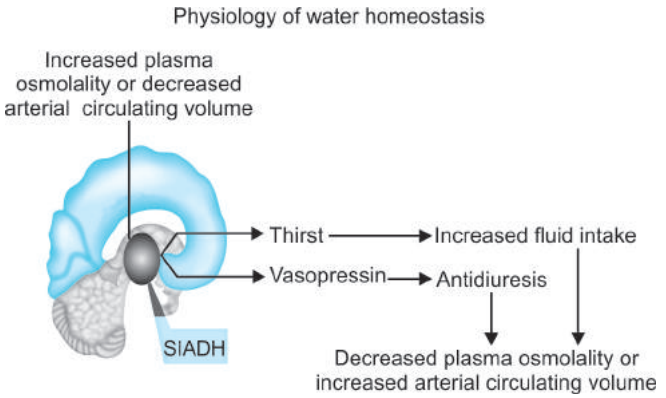


Fig. 3: Water homeostasis.

when P-[Na^+] increases. Vasopressin release can also be stimulated nonosmotically by a reduced effective circulating volume, stress, pain, nausea, vomiting, various drugs and exercise.

Irrespective of vasopressin, the kidney's ability to excrete water is influenced by solute intake (protein/urea and cations).

A low solute intake reduces urine solute excretion and thereby urine volume despite maximally diluted urine. In contrast, a high protein/urea intake or generation will increase the urine volume.

CLASSIFICATION

Hyperosmolar

Osmotically active substances confined to the extracellular/plasma compartment cause a shift of water from the intracellular compartment, for example, hypertriglyceridemia, hyperglycemia (P-[Na^+] is reduced by 2.4 mEq/L per 100 mg/dL increase in P-[Glc]), mannitol infusion.

Iso-osmolar

Pseudohyponatremia is an unusual measurement flaw in patients with hyperlipidemia/hyperproteinemia whose plasma tonicity is normal.

Hypo-osmolar

The most common and clinically relevant variety of hyponatremia which is associated with a fall in P-[Na^+].

by mansdocs.com

Hypo-osmolar hyponatremia can be further classified in Table 1.

MANAGEMENT

First and foremost is to determine whether acute correction is required. This decision is made based on the patient's symptoms at a time when the mechanisms causing the hyponatremia are rarely known (Box 1).

Treatment should be guided by the patient's symptoms and not by the assumed acute (<48 hours) or chronic nature of hyponatremia. There is no set P-[Na^+] level below which severe symptoms arise. Cellular swelling in the brain edema corresponds with the relative reduction and rapidity of fall of P-[Na^+] rather than an arbitrarily defined absolute P-[Na^+] value.

Hyponatremia with Severe Symptoms—Airway, Breathing, Circulation and 3% NaCl Bolus Therapy

The neurologic manifestations of hyponatremia appear to be entirely due to the consequences of plasma hypo-osmolality. A fall in plasma osmolality causes water movement from the extracellular space into cells. The resulting increase in cell water can lead to brain swelling (Flowchart 1). ICP rises when the brain cells swell in the rigid skull. Because severe cerebral symptoms indicate ongoing brain damage and a substantial risk of incarceration, treatment should not be delayed.

Secondary brain damage caused by hypoxia, hypercapnia and hypoperfusion should be avoided with an ABC approach. Lab samples for plasma osmolality, urine osmolality and urine spot sodium should be sent before initiating therapy. Immediate ICP reduction is best induced with one or more boluses of 2 mL/kg 3% NaCl (or a corresponding amount of more hypertonic NaCl) given intravenously/intraosseously. The effect is immediate, and bolus doses may be repeated at 5-minute intervals. One 2 mL/kg 3% NaCl bolus causes a controllable rise in P-[Na^+] of about 2 mmol/L. Cerebral symptoms decrease when P-[Na^+] increases by 4 to 6 mmol/L. Infusion of 0.9% NaCl should not be used as it does not cause an immediate, controllable increase in P-[Na^+], and 0.9% NaCl might worsen the hyponatremia in Syndrome of inappropriate ADH (SIADH).

Other conditions like cerebral disease, hepatic encephalopathy should be considered if the patient fails to respond, and a maximum of three boluses should be given.

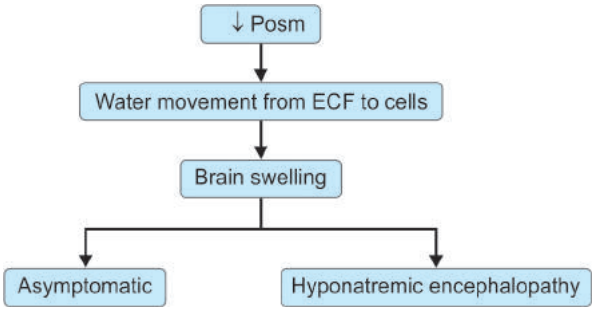
Table 1: Causes of hypo-osmolar hyponatremia.

Hypervolemic	*Hypovolemic*		*Isovolemic*
	Urine [Na^+] < 15 mEq/L	*Urine [Na^+] > 20 mEq/L*	
• Heart failure • Cirrhosis • Nephritic syndrome • Renal failure	• Vomiting, diarhea, fistula • External loss • Pancreatitis, peritonitis	• Salt wasting nephropathy • Hypoaldosteronism • Recent diuretic use specially thiazide	• SIADH • Cortisol deficiency • Hypothyroidism • Psychogenic polydipsia • Beer drinkers hyponatremia

Box 1: Cerebral sysmptoms in hyponatremia.

Severe symptoms
• Decreased consciousness
• Seizures
• Muscle rigidity
Other symptoms
• Nausea and vomiting
• Headache
• Bloating, 'puffiness'
• Muscle weakness, cramps or spasms

Flowchart 1: Effect of hyponatremia on brain.



by mansdocs.com

Vasopressin V_2-receptor antagonists are not recommended as they do not induce a controllable and fast increase in P-[Na^+] and the induction/worsening of hypovolemia can be hazardous (Flowchart 2).

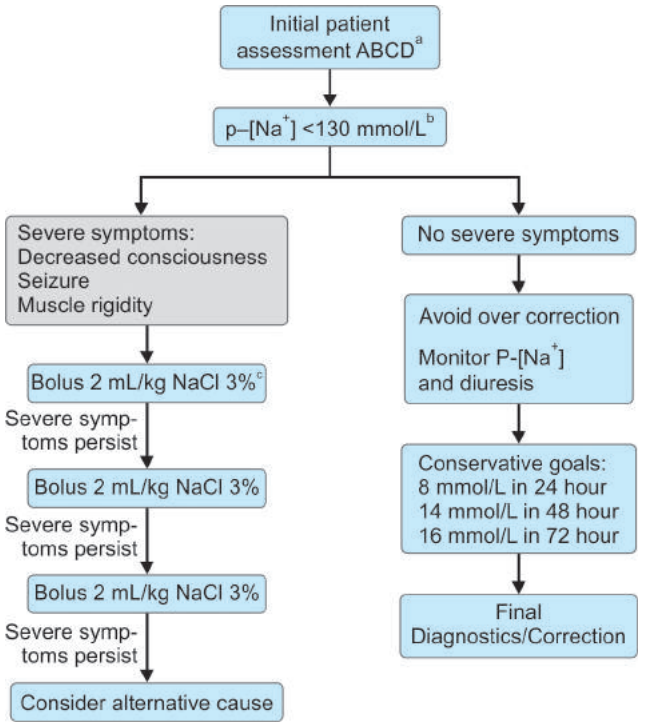
Treatment of Hyponatremia without Severe Symptoms

Choice of therapy is governed by the cause of hyponatremia.

Salt Infusions

- Normal saline/hypertonic saline
- True volume depletion
- Diuretic therapy, provided the diuretic is no longer acting
- Adrenal insufficiency, in which cortisol replacement is also indicated.

Flowchart 2: Management of symptomatic hyponatremia.



([a]) A = Airway, B = Breathing, C = Circulation, D = Disability: Avoid secondary brain damage. Diagnose hypo-/hyperglycemia.
([b]) Higher levels in patients with intracranial pathology/known hypernatremia.
([c]) Bolus = peripheral or central intravenous/intraosseous infusion in a few minutes. Response to a bolus is observed after 5 minutes: if symptoms decrease, go to "no severe symptoms"; if severe symptoms persist, infuse a maximum of three boluses. Corresponding amounts of more concentrated NaCl can be used.

Fluid Restriction

- Primary polydipsia
- Edematous states such as heart failure and hepatic cirrhosis SIADH
- Advanced chronic kidney disease.

Diuretic Therapy

- Congestive heart failure (CHF)
- Cirrhosis
- Nephrotic syndrome
- Sepsis.

ADH-V_2 (Antidiuretic) Receptor Antagonist

- SIADH
- CHF
- Liver Failure.

HOW TO GIVE SALINE CORRECTION

Central Pontine Myelinolysis

Rapid correction of severe hyponatremia may lead within one to several days to the development of a neurologic disorder called osmotic demyelination or central pontine myelinolysis detectable by cerebral computed tomography or magnetic resonance imaging.

The mechanisms responsible for osmotic demyelination are not completely understood. Rapid elevation in the plasma Na^+ concentration leads to water movement out of the brain, which can lower the brain volume below normal. Such osmotically induced shrinkage in axons could sever their connections with surrounding myelin sheaths. Alternatively, the initial brain cell response to brain shrinkage may be the uptake of potassium and sodium from the extracellular fluid; this elevation in cell cation concentration could be toxic to the cells.

Manifestations include mental status changes, dysarthria, dysphagia, paraparesis or quadriparesis, and coma; seizures may occur but are less common.

RISK FACTORS

- Increase S. Na greater than 20 mEq/L in the first 24 hours
- Absolute rise to greater than 140 mEq/L
- Patients with liver disease are particularly susceptible.

Recommendations

Asymptomatic patient: Plasma Na^+ concentration be raised at a maximum rate of 12 mEq/L/day (which represents an average correction of 0.5 mEq/L/h).

by mansdocs.com

Box 2: Example of sodium correction.

60 kg/female/Na^+–110
Raise 10 mEq/L over next 24 hour
Target –120 mEq/L
Deficit = 120 – 110 = 10
TBW = 60 × 0.5 = 30
{Na^+} = Deficit × TBW = 300 mEq
0.9% saline-154 mEq/l
(Give 2 liter over 24 hour)
3% saline-500 mEq/l
(Give 600 mL over 24 hour)

TBW = 0.5 × lean body weight (women)
0.6 × lean body weight (men)

Symptomatic patient: More aggressive initial correction, at a rate of 1.5–2.0 mEq/L/hour, is indicated for the first 3–4 hours (or until the symptoms resolve, the plasma Na^+ concentration should probably not be raised by more than 12 mEq/L in the first 24 hour (Box 2).

DIAGNOSTIC WORKUP

Three laboratory findings provide important information in the differential diagnosis of hyponatremia: (1) Posm, (2) Uosm and (3) urinary Na^+ concentration.

Plasma Osmolality

Because Posm is mainly determined by the plasma Na^+ concentration, it is reduced in most hyponatremic patients. In some cases, however, the Posm is either normal (pseudohyponatremia) or elevated (hyperosmolar hyponatremia).

Urine Osmolality

In patients with hypo-osmolar hyponatremia, the Uosm can be used to distinguish between patients with impaired water excretion, accounting for most cases, and primary polydipsia, in which water excretion is normal but intake is so high that it exceeds excretory capacity. Hyponatremia caused by primary polydipsia should completely suppress ADH secretion, resulting in the excretion of maximally dilute urine with an osmolality less than 100 mOsm/kg and a specific gravity less than 1.003. A higher Uosm indicates an inability to excrete free water normally, which suggests continued secretion of ADH.

Urinary Na^+ Concentration

The two major causes of hyponatremia are (1) hypovolemia and (2) SIADH. These disorders can usually be distinguished by measuring the urinary Na^+ concentration.

Fractional Excretion of Sodium

The fractional excretion of sodium (FENa) is a more accurate assessment of volume status than the urinary Na^+ concentration in patients with acute kidney injury; an FENa less than 1% suggests effective volume depletion. The random urinary Na^+ concentration is more accurate for assessing the volume status in patients with hyponatremia with a normal plasma creatinine concentration. The FENa should generally not be used in this setting.

SPECIAL SCENARIO

SIADH

Hyponatremia in SIADH results primarily from ADH-induced retention of ingested water. Appropriate therapy in this disorder depends on the severity of the hyponatremia and on the fact that, although water excretion is impaired, sodium handling is intact because there is no abnor-mality in volume-regulating mechanisms such as the renin-angiotensin aldosterone system. Water restriction is the mainstay of therapy in asymptomatic hyponatremia of chronic SIADH. The associated negative water balance raises the plasma Na^+ concentration toward normal.

Severe, symptomatic, or resistant hyponatremia often requires the administration of salt. If the plasma Na^+ concentration is to be elevated, the osmolality of the fluid given must exceed that of the urine. Correction of the hyponatremia in these cases requires the administration of hypertonic 3% saline intravenously or salt tablets orally, preferably in combination with a drug that lowers the Posm, loop diuretic are most often used for this purpose. Administering a fluid with an osmolarity less than urine osmolarity may actually worsen hyponatremia.

Specific antagonists to the ADH-V_2 (antidiuretic) receptor in the cortical collecting tubule have shown promise and two have now been approved for clinical use. For example, conivaptan, an antagonist to both the V_1 (vascular) and V_2 (ADH) receptors, tolvaptan is an oral ADH antagonist which is specific for the V_2 receptor.

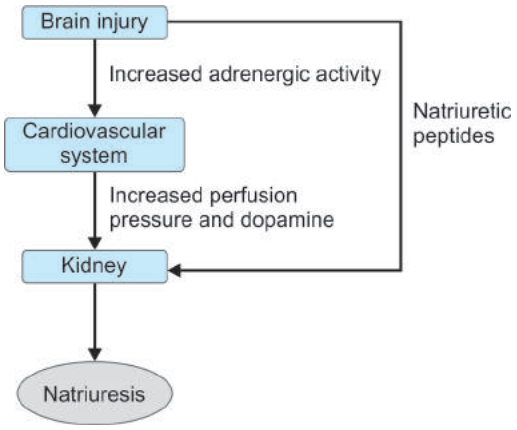
Cerebral Salt Wasting Syndrome

Neurosurgery and central nervous system trauma, especially subarachnoid hemorrhage, may be associated with excessive renal Na^+ excreation. The loss of Na^+ results in volume depletion, which leads to "nonosmotic"

by mansdocs.com

release of ADH. This volume depletion is the main feature that distinguishes cerebral salt wasting from SIADH (Flowchart 3).

Flowchart 3: Mechanism of cerebral salt wasting.



Management centers on correction of intravascular volume depletion and hyponatremia, as well as on replacement of ongoing urinary sodium loss, usually with intravenous hypertonic saline solutions.

BIBLIOGRAPHY

1. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000; 342:1581-9.
2. Arora SK. Hypernatremic disorders in the intensive care unit. J Intensive Care Med. 2013;28(1):37-45.
3. Irwin RS, Rippe JM (Eds). Intensive Care Medicine. Lippincott Williams & Wilkins; 2011.
4. Lindner G, Funk GC. Hypernatremia in critically ill patients. J Critical Care. 2013;28:216.e11-20.
5. Overgaard-Steensen C, Ring T. Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. Crit Care. 2013;17:206.
6. Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH versus CSW. Trends Endocrinol Metab. 2003;14(4):182-7.

by mansdocs.com

CHAPTER

36

Disorders of Calcium and Magnesium

Khalid Khatib, Subhal Dixit, Kapil Borawake

INTRODUCTION

Abnormalities of calcium and magnesium metabolism occur frequently in patients admitted to intensive care units (ICU). Infrequently, they may be the primary cause for hospitalization, but more often they complicate existing medical conditions.[1] A thorough understanding of the symptoms which are usually nonspecific and accurate early diagnosis and appropriate treatment of the abnormal cation metabolism will prevent additional morbidity and mortality in the already fragile population of ICU patients.

CALCIUM METABOLISM

Functions of calcium:[1,2] Calcium is required in the body for

- Contractions of muscles (skeletal, smooth, cardiac)
- Impulse conduction within nerves
- Release of hormones in response to stimuli
- Coagulation of blood
- Activation of protein kinases and enzyme phosphorylation.

Calcium acts as a second messenger inside the cell to perform the above functions. It is also involved in the activation of other intracellular messengers like cAMP and inositol-1,4,5-triphosphate, thus mediating the responses of various hormones like epinephrine, glucagon and vasopressin.[3]

Calcium homeostasis: The serum levels of calcium are maintained in a very narrow range for the optimal functioning of the various processes that require its presence. Calcium is transported in the plasma: (1) bound to albumin (45%), (2) bound to anions—phosphates and citrates (10%) and (3) in free and ionized state-ionic calcium (45%).[4] Only the calcium in ionic state is active. The normal serum calcium level (ionized + bound) ranges between 8.8 mg/dL and 10.4 mg/dL (2.2–2.6 mmol/L). The normal serum ionized calcium level ranges between 4.65 mg/dL and 5.25 mg/dL (1.16–1.31 mmol/L).[3]

Relation of serum albumin and serum calcium: For every 1 g/dL reduction in serum albumin level, there is a fall of approximately 0.8 mg/dL of the serum total calcium level. Thus in conditions with abnormal level of serum albumin, the measured calcium level needs to be corrected for the level of albumin. (Add 0.8 mg/dL to measured serum calcium level for every 1 g/dL reduction of serum albumin level below 4 g/dL). Thus, in conditions like volume overload, chronic illness, malnutrition or nephrotic syndrome, which are usually associated with hypoalbuminemia, the measured total serum calcium level may need to be corrected for the level of serum albumin. In these conditions, it is better to measure the serum ionized calcium level which is independent of the serum albumin level.

Acid base disturbances and serum calcium: There is an increase in the serum calcium level with acidosis and decrease in the serum calcium level with alkalosis.

Regulation of serum calcium: The major factors regulating serum calcium level are:

- Parathyroid hormone (PTH)—through effects on bone, kidney and gastrointestinal tract (GIT).
- Vitamin D—through effects on bone, kidney and GIT.

by mansdocs.com

- Calcium—acting via a calcium sensing receptor (CaSR) in the parathyroid gland and in the loop of Henle in the kidneys.[5]

PTH and serum calcium:[1-3,6,7] Even a small reduction in the serum level of calcium is detected by the CaSR leading to an almost instantaneous secretion of PTH by the parathyroid glands. PTH leads to resetting of the calcium level towards the normal range via three mechanisms: (1) Reduced urinary calcium excretion; (2) Increased intestinal absorption of calcium due to increased production of 1, 25-dihydroxy Vitamin D3 (calcitriol) by the kidneys and (3) Increased bone resorption.[5]

DISORDERS OF CALCIUM METABOLISM

Hypocalcemia

It is defined as a level of serum total calcium less than 8.5 mg/dL.

Causes:[2,4,7] The common causes of hypocalcemia are:

- *Hypoparathyroidism*: (a) hereditary, (b) acquired and (c) pseudo
- *Renal failure*: (a) acute and (b) chronic
- Intestinal malabsorption
- Nutritional deficiency of calcium
- *Vitamin D dependent rickets*: (a) Type I and (b) Type II
- *Common causes of hypocalcemia in the ICU*: (a) Alkalosis acute, (b) massive blood transfusion, (c) cardiopulmonary bypass, (d) hypomagnesemia, (e) pancreatitis, (f) acute renal insufficiency, (g) sepsis, (h) severe acute hypophosphatemia, (i) rhabdomyolysis, (j) drugs—aminoglycosides, heparin, theophyllin, bisphosphonates cinacalcet and foscarnet and (k) spurious hypocalcemia due to gadolinium based contrast agents—gadodiamide and gadoversetamide.[8-10]

Signs and symptoms: The clinical features of hypocalcemia are:

- *Neuromuscular manifestations*: (a) Tetany: manifested by Chvostek's sign—tapping the facial nerve causes spasm of the facial muscles, and Trousseau's sign—inflation of applied blood pressure cuff to level above systolic blood pressure for 3 minutes causing carpopedal spasm, and is a manifestation of cell membrane instability; (b) hyperreflexia, (c) paresthesias, (d) laryngeal stridor and (e) seizures.
- *Cardiovascular manifestations*: (a) prolonged QT interval, (b) complete heart block and (c) ventricular ectopy, ventricular tachycardia and ventricular fibrillation.

Diagnosis: The serum level of calcium (either total or ionic calcium) needs to be measured.

The following precautions are to be taken during handling of blood sample sent to laboratory for estimation of serum calcium: (1) Avoid presence of gas bubbles in the blood sample; (2) Do not send the sample in citrate or EDTA container; (3) Use of heparinized syringe for collecting and transporting the blood sample to the laboratory is preferred.[7]

Treatment

- If possible, identify and treat the cause.[11]
- Acute, symptomatic, severe hypocalcemia is treated with calcium gluconate, administered by intravenous infusion (bolus—10 mL of 10% solution diluted in isotonic saline or 5% dextrose, and then continuous infusion of 1–2 mg of elemental calcium/kg/h for 6–12 hours, to maintain serum calcium level in normal range.
- *Chronic hypocalcemia*: (a) Treat the cause. (b) Oral calcium therapy—2–4 g/day of elemental calcium as its carbonate, gluconate, lactate or citrate salt; (c) Vitamin D—as calcitriol 0.25–1 mcg/day; (d) Thiazide diuretics—hydrochlorozide 12.5–25 mg/day and act by decreasing urinary losses of calcium.

Hypercalcemia

An increase in the serum level of calcium may be (1) Mild: 10.1–12.0 mg/dL (2) Moderate: 12.0–14.0 mg/dL or (3) severe: More than 14.0 mg/dL.[12]

Causes: The causes of hypercalcemia are:

- *Hormone or vitamin mediated*: (a) PTH excess: (1) primary hyperparathyroidism—due to single parathyroid adenoma, hyperplasia of all parathyroid glands, parathyroid cancer or as part of MEN Type 1 and 2A; (2) tertiary hyperparathyroidism; (3) familial hypercalciuric hyper, calcemia, (b) thyrotoxicosis, (c) adrenal insufficiency, (d) vitamin D—Exogenous excess Vitamin D or patient undergoing hemodialysis and (e) Vitamin A toxicity
- *Malignancy*: (a) multiple myeloma, (b) parathyroid hormone-related peptide (PTHp) secreting malignancies of breast, kidneys, and lungs, (c) bone metastases and (d) Lymphoma
- *Drugs*: (a) lithium, (b) thiazides
- *Others*: (a) sarcoidosis, (b) Milk Alkali syndrome and (c) Paget's disease

by mansdocs.com

Symptoms and Signs: These depend on the level of serum calcium and the rate of rise. The clinical features of hypercalcemia are:

- *Central nervous system*: (a) lethargy, (b) confusion, altered mental status, (c) memory impairment, (d) psychiatric manifestations—depression, (e) stupor and (f) coma.
- *Cardiac*: (a) short QT interval and (b) hypertension.
- *Gastrointestinal tract*: (a) anorexia, (b) vomiting, (c) constipation and (d) peptic ulcer.
- *Renal*: (a) polyuria, (b) nephrolithiasis, (c) nephrocalcinosis, (d) nephrogenic diabetes insipidus, (e) acute renal failure, (f) chronic renal failure and (g) renal tubular acidosis Type II.
- *Musculoskeletal*: (a) fatigue, (b) muscle weakness and (c) bone pain.

Diagnosis: Parathyroid adenoma is suspected as the cause of hypercalcemia when high or normal PTH level is found in the presence of hypercalcemia. Further investigations are warranted in the form of ultrasonography of the neck and sestamibi nuclear scan to locate the parathyroid adenoma. Malignancy is suspected as the cause of hypercalcemia if the PTH is low or near normal. In this setting, a normal anion gap and abnormal serum electrophoresis with M band will direct towards multiple myeloma. Exogenous Vitamin D is suspected as the cause of hypercalcemia if serum 25-hydroxy Vitamin D is elevated while elevated calcitriol make a diagnosis of sarcoidosis more likely.

Treatment

- Identify and treat the cause.
- *Hydration*: (a) should be rapid, (b) up to 2–4 liters over 24 hours intravenously for 1–3 days and (c) enhances filtration and excretion of calcium.
- *Loop diuretics (Furosemide)*: (a) Dose: 10–20 mg intravenously, repeated every 6 hours, after adequate hydration, till the calcium level returns to normal. In patients with renal insufficiency, higher dose (up to 100–200 mg) may be required. (b) They enhance calcium excretion and prevent fluid overload due to excessive hydration. (c) They may cause hypokalemia.
- *Bisphosphonates (Zoledronic acid, Pamidronate)*:[4,11,12] (a) Dose: Zolendronic Acid—4 mg intravenously, over 15–30 minutes. Pamidronate—60–90 mg intravenously, over 2–4 hours. (b) The onset of action is after 4–7 days. (c) They are treatment of first choice in hypercalcemia associated with malignancy. (d) The mechanism of action is by inhibition of bone resorption and they provide sustained reduction in serum calcium level. (e) Adverse reaction: They may cause nephrotoxicity. (f) Treatment may have to be repeated after a couple of weeks.
- *Calcitonin*: (a) Dose: 4–8 units/kg, intramuscular or subcutaneous, 6 hourly for 24 hours. (b) It inhibits bone resorption and produces an acute reduction in serum calcium levels. (c) Adverse reaction: It may cause nausea, vomiting and cramps. (d) Its effects are limited by tachyphylaxis.
- Gallium nitrate, plicamycin and steroids.
- Hemodialysis: (a) Low calcium dialysate is used. (b) It is done when reduction in serum calcium level is urgent and when all else fails.
- Calcium receptor antagonist (Cinacalcet): (a) It is used in the treatment of secondary and tertiary hyperparathyroidism.[13]

MAGNESIUM METABOLISM

Magnesium is a cation found in abundance throughout the human body, second only to potassium. It acts in many enzymatic reactions as a co-factor, especially reactions involving adenosine triphosphate (ATP). Magnesium is involved in maintaining the normal function of cell membrane and maintaining neuromuscular excitability.[14] The magnesium in the body is distributed into bones (60%), muscles (20%), soft tissue (20%) and extracellular fluid (1%). Out of the 1% in the ECF, about 20% is bound to proteins while the remaining 80% is in the unbound (ionic) form. Thus, the serum magnesium level measures less than 1% of the total body magnesium and is a poor indicator of total body store of magnesium.[4,14] The normal plasma magnesium level is 1.7–2.4 mg/dL (1.5– 2.0 mEq/L).[15,16] The maintenance of serum magnesium level within this narrow band is a function of its absorption through the GIT (30–40% of dietary magnesium is absorbed) and its excretion in the kidneys (around 2% is excreted). The level of absorption and excretion will vary inversely according to the serum levels of magnesium. Thus, if the serum level of magnesium is increased, absorption will reduce and excretion will increase and vice-versa.[4]

DISORDERS OF MAGNESIUM METABOLISM

Hypomagnesemia

It is defined as serum magnesium level less than 1.3 mg/dL or 0.7 mmol/L or 1 mEq/L and is associated with a urinary magnesium level of less than 0.5 mmol/L or mEq/L.[16,17]

by mansdocs.com

Table 1: Treatment of hypomagnesemia.

	Symptoms and ECG changes	*Normal renal function*	*Intestinal malabsorption*	*Treatment*
Asymptomatic hypomagnesemia	No	Yes	No	Oral magnesium 240–720 mg/day in divided doses Side effects-diarrhea
Symptomatic, hypomagnesemia with normal renal function	Yes	Yes	No/Yes	1–2 g $MgSO_4$ i.v. over 15 mins followed by i.v. infusion of 6 g $MgSO_4$ in 1,000 mL of NS or 5% dextrose over 24 hours for 3–7 days. Check Mg levels every day
Hypomagnesemia with renal insufficiency	Yes/No	No	Yes/No	No bolus dose, 2–3 g $MgSO_4$ in 50–100 mL NS or 5% Dextrose over 24 hours

Causes: The causes of hypomagnesemia are:

- *Impaired absorption through GIT*: (a) starvation, (b) diarrhea (c) pancreatitis, (d) GIT fistula, (e) short bowel syndrome and (f) prolonged nasogastric suction.
- *Drugs*: (a) furosemide, (b) aminoglycosides (c) amphotericin B, (d) cyclosporin and (e) cisplatin.
- *Toxins*: Alcohol
- *Diabetes mellitus*: During treatment of diabetic ketoacidosis.[17]
- *Magnesium wasting syndrome*:[18-21] (a) Bartter's syndrome, (b) Gitelman's variant of Bartter's syndrome, (c) familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHC) and (d) Claudin-16 mutation, *TRPM6* gene mutation.
- *Renal*: (a) postobstructive dieresis, (b) acute tubular necrosis, (c) tubulointerstitial disease, (d) glomerulonephritis and (e) pyelonephritis

Signs and Symptoms

- *Central nervous system*: (a) lethargy, (b) confusion, (c) tremors, (d) fasciculations, (e) nystagmus, (f) tetany, (g) ataxia and (h) seizures.
- *Cardiac*: (a) sinus tachycardia, (b) supraventricular tachycardia and (c) ventricular ectopy, tachycardia and fibrillation.

Diagnosis

- Serum magnesium—levels are usually low but may be normal even when there is depletion of total body magnesium.
- 24-hours urinary magnesium excretion—if it is more than 2% suggests a renal cause for hypomagnesemia.
- Fractional excretion of magnesium—if it is more than 2% suggests a renal cause for hypomagnesemia.
- Electrocardiogram—will reveal prolonged PR and/or QT intervals, T wave abnormalities, wide QRS complexes and Torsades de pointes.

Treatment: The treatment of hypomagnesemia is supplementation of magnesium—the route and quantity depend on the presence or absence of renal insufficiency, intestinal malabsorption and symptoms. Table 1 summarizes the treatment of hypomagnesemia in various scenarios. The serum magnesium level should not exceed 2.5 mEq/L and deep tendon reflexes are monitored.

Hypermagnesemia: It is defined as serum magnesium level exceeding 2.2 mEq/L.

Causes[22]

- Renal failure (a) acute and (b) chronic.
- Overuse of magnesium containing laxative.
- Parenteral treatment with magnesium (eclampsia).
- Use of magnesium sulfate enema.
- Milk-Alkali syndrome

Signs and symptoms: The clinical features of hypermagnesemia depend on the serum magnesium level.

There are usually no symptoms till serum magnesium levels reach 3 mEq/L. Nonspecific symptoms like lethargy, nausea, flushing, and headache are observed once serum magnesium levels exceed 4–6 mEq/L. Once the serum magnesium level reach 6–9 mEq/L, there will be loss of deep tendon reflexes associated with somnolence, hypotension and ECG changes. Once the serum magnesium levels exceed 10 mEq/L, it manifests with paralysis, respiratory distress and failure, complete heart block and cardiac arrest.

Treatment

- Identify at-risk patients.
- Hypermagnesemia can be prevented by reducing the consumption of magnesium containing products.
- Ten percent calcium gluconate, 10–20 mL intravenously over 10–15 minutes will counter the effects of high levels of magnesium.

by mansdocs.com

- Hemodialysis may be needed to remove excess magnesium in certain patients with chronic kidney disease.
- Mechanical ventilation and temporary pacemaker in a fraction of patients with very high levels of magnesium.

REFERENCES

1. Fink MP, Abraham E, Vincent JL, et al. Hypocalcemia and hypercalcemia. Textbook of Critical Care, 5th Edition. Philadelphia: Saunders, An imprint of Elsevier; 2005. pp.79-81.
2. Irwin RS, Rippe JM. Disorders of mineral metabolism. Irwin and Rippe's Intensive Care Medicine, 7th Edition. Philadelphia: Lippincott, Williams & Wilkins; 2012.
3. The Merck Manual Professional Edition. [online] Available from http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/electrolyte_disorders/hypocalcemia.html. [Accessed Jan. 2015].
4. Ghosh AK, Joshi SR. Disorders of calcium, phosphorus and magnesium metabolism. J Assoc Physicians India. 2008;56:613-21.
5. Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol.. 2010;298:F485-99.
6. Kumar R. Vitamin D and calcium transport. Kidney Int. 1991;40:1177-89.
7. Kollef M, Isakow W. Electrolyte abnormalities. The Washington manual of critical care, 2nd Edition. Philadelphia: Lippincott, Williams & Wilkins; 2012. pp. 178-208.
8. Gandhi MJ, Narra VR, Brown JJ, et al. Clinical and economic impact of falsely decreased calcium values caused by gadoversetamide interference. AJR Am J Roentgenol. 2008; 190:W213-7.
9. Doorenbos CJ, Ozyilmaz A, van Wijnen M. Severe pseudohypocalcemia after gadolinium-enhanced magnetic resonance angiography. N Engl J Med. 2003;349:817-8.
10. Prince MR, Erel HE, Lent RW, et al. Gadodiamide administration causes spurious hypocalcemia. Radiology. 2003; 227:639-46.
11. Bushinsky DA,Monk RD. Electrolyte quintet: Calcium. Lancet. 1998;352:306-11.
12. Carroll MF, Schade DS. A practical approach to hypercalcemia. Am Fam Physician. 2003;67:1959-66.
13. Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350:1516-25.
14. Limaye CS, Londhey VA, Nadkar MY, et al. Hypomagnesemia in critically ill medical patients. J Assoc Physicians India. 2011;59:19-22.
15. Marino P. Fluid and electrolyte disorders—magnesium. The ICU book, 2nd Edition. Philadelphia: Lippincott Williams & Wilkins; 2004. pp. 660-72.
16. al-Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24:737-52.
17. Paymaster NJ. Magnesium metabolism: a brief review. Ann R Coll Surg Engl. 1976;58:309-14.
18. Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996;12:24-30.
19. Simon DB, Karet FE, Hamdan JM, et al. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. Nat Genet. 1996;13:183-8.
20. Müller D, Kausalya PJ, Meij IC, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: blocking endocytosis restores surface expression of a novel Claudin-16 mutant that lacks the entire C-terminal cytosolic tail. Hum Mol Genet. 2006;15:1049-58.
21. Schlingmann KP, Sassen MC, Weber S, et al. Novel TRPM6 mutations in 21 families with primary hypomagnesemia and secondary hypocalcemia. J Am Soc Nephrol. 2005;16: 3061-9.
22. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. Lancet. 1998;352:391-6.

by mansdocs.com

SECTION 6

Neurological Care

by mansdocs.com

by mansdocs.com

CHAPTER

37

Management of Critically Ill Trauma Patients

Babita Gupta

INTRODUCTION

Trauma is among the leading causes of mortality in all age groups all over the world, mainly affecting the young and most productive persons of the society. It often leads to long-term morbidity and permanent disability in those who survive. According to the statistics of World Health Organization (WHO), around 5.8 million people die annually all over the world as a result of trauma. This accounts for around 12% of the world's burden of disease. It has been projected that trauma will be the third largest cause of mortality in developing countries by the year 2020. In India, a trauma related death occurs in every 1.9 minutes.

Trauma may be accidental, homicidal or suicidal. The pattern of trauma varies widely. The common injury patterns include blunt trauma which is mainly due to motor vehicular accidents and falls and penetrating trauma which is often associated with assaults and self-inflicted injuries. Blast can cause blunt as well as penetrating injuries along with burns.

Death from trauma has a trimodal distribution pattern which implies that death due to injury occurs in one of three peaks or periods (Fig. 1). The first peak occurs in seconds to minutes of injury and is mainly due to hypoxia, rupture of heart or any injury to any great vessel. Prevention is the only means to reduce this peak of trauma related mortality. The second peak occurs within minutes to hours post injury and is mainly due to traumatic brain injury (TBI), injury to the chest, abdomen, pelvic fractures, and/or multiple other injuries causing severe blood loss. The concept of "Golden Hour" care introduced by R

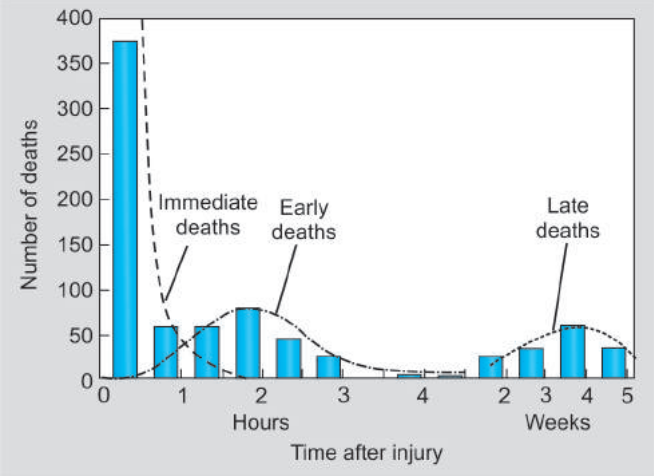


Fig. 1: Trimodal death distribution of trauma patients.
Source: Permission from American College of Surgeons, Committee on Trauma Reqd.

Adams Cowley is characterized by the need for rapid assessment and simultaneous resuscitation within first hour of injury. This is the fundamental teaching of the advanced trauma life support (ATLS), which is conducted under the auspices of American College of Surgeons (ACS). ATLS training program and following their treatment principles has shown to reduce mortality in trauma patients. The third peak of death occurs days to weeks after the initial injury, with sepsis and multi-organ dysfunction syndrome (MODS) being the most common cause. Meticulous examination, timely decision making and adequate resuscitative steps undertaken during each of the preceding periods influences the outcome during this stage.

by mansdocs.com

The continuum care of a trauma patient begins right from the time of injury to the emergency room (ER), continues in the operation room (OR) and many a times extends in the intensive care unit (ICU). Prompt recognition and management of immediate life threatening injuries and skillful decisions during prehospital transport, in ER, OR and in ICU can have far reaching beneficial consequences.

GENERIC APPROACH TO TRAUMA CARE

The ATLS curriculum of the ACS has described the prioritization of trauma care and developed a systematic approach of evaluation and resuscitation for this purpose. These principles of trauma management stand out as pillars in trauma system design; understanding which a critical care specialist has to determine his optimum role in the multispecialty effort for achieving the goal of patient survival. As a member of the emergency team, he has to extensively follow the systematic approach of evaluation as enumerated in ATLS course, along with resuscitative efforts. It is beyond the scope of this chapter to describe initial assessment of a trauma patient in detail. This chapter enumerates the basic principles of the initial approach to a trauma patient as recommended by ATLS which would help a trauma critical care specialist in managing a critically ill patient. Treatment of a severely injured patient requires rapid assessment and resuscitation in a systematic and prioritized manner. This approach is termed as initial assessment and mainly includes

- Preparation
- Triage
- Rapid primary survey
- Resuscitation of vital functions
- Detailed secondary survey
- Definitive care

Tertiary survey, which is done at later stage, and is an ongoing process to diagnose and manage injuries and their complications.

PREPARATION

The resuscitation bay in the ER as well as the OR should be adequately equipped with properly functioning resuscitation equipment including difficult airway cart and should be kept at a place where it is easily accessible and readily available. All the monitoring devices should be checked; warm intravenous fluids and emergency drugs should be immediately available. All the personnel taking care of trauma patient must protect themselves from communicable diseases, like hepatitis and acquired immunodeficiency syndrome by wearing standard protective devices which include face mask, protective eye wear, shoe cover, water proof gown and gloves.

TRIAGE

Several patients with diverse type of injuries may present simultaneously in a busy ER. Some patients may have life-threatening injuries requiring immediate intervention and some may have trivial injury which can be managed later. Hence, it is essential to triage patients, according to the severity of injury and clinical condition of the patient. The word triage means 'to sort' which in ER setting categorizes the patients into emergent, urgent and nonurgent. Emergent patients are the patients who are severely injured and have life threatening conditions. These patients have the highest priority and should be managed immediately. Urgent patients have serious injuries but do not have immediate life threatening conditions. Non-urgent patients have minor injuries and can be addressed after emergent and urgent patients have been taken care of. However, it is important to reassess and retriage the patients repeatedly and manage accordingly.

PRIMARY SURVEY

A rapid and efficient assessment of the vital functions of a multiply injured patient in a systematic way with establishment of treatment priorities based on their injuries and mechanism of injury are the key principles in primary survey. This process begins with the ABCDE of trauma care, which guides the identification of life threatening conditions by adhering to the initial assessment sequence of

A: Airway maintenance with cervical spine protection
B: Breathing and ventilation
C: Circulation with hemorrhage control
D: Disability: Neurologic status
E: Exposure/Environmental control. Expose the patient, however prevent hypothermia

The order of priority is based on the fact that the abnormality which poses the greatest threat to life should be addressed first. A rapid method for assessment of the A, B, C and D includes verbal communication with the

by mansdocs.com

patient, and asking his name and mechanism of injury. An appropriate response ensures that airway is not compromised at least for the time being, breathing is not severely compromised, cerebral perfusion is maintained and there is no major decrease in level of consciousness. A patient who fails to respond or gives an inappropriate response suggests an altered level of consciousness, airway and ventilatory compromise or both and indicates further evaluation.

Airway with Cervical Spine Control

To establish and maintain a patent airway remains the highest priority in management of trauma patient since hypoxemia can cause irreversible brain injury and death within minutes. The airway should be assessed to ascertain patency. Assessment for airway obstruction includes inspection for foreign bodies and facial, mandibular, or tracheal/laryngeal injuries which result in airway obstruction. The clinical manifestations of compromised airway include choking, apprehensive appearance, refusing to lay flat, noisy breathing, inspiratory and expiratory stridor, labored breathing, use of accessory muscles (suprasternal and intercostal retraction, flaring nostrils), anxiety and obtundation. It is important to remember that agitated and abusive patient might be hypoxic and obtundation of reflexes could be due to hypercarbia and should not be mistaken for drug/alcohol intoxication. Cyanosis and loss of consciousness ensues as hypoxia worsens and are late signs; action must be taken before these manifestations develop. Pulse oximetry should be used early in the airway assessment to detect inadequate oxygenation.

Supplemental oxygen by high flow oxygen mask (12–15 liter/ min should be provided to all patients. Foreign body, blood, vomitus or secretions should be suctioned out with a wide bore rigid suction cannula.

The jaw thrust or chin lift maneuver are the airway maneuvers which can be used in trauma patients to relieve the airway obstruction. The airway maintenance techniques help in lifting the tongue away from the hypopharynx. The triple airway maneuver, which involves slight extension of the neck, is not recommended in trauma patients.

Jaw-thrust maneuver: One hand is placed on each side of the patient's jaw and angles of patient's lower jaw are grasped and lifted, hence displacing the mandible forward (Fig. 2).

Chin-lift maneuver: In this maneuver the chin is lifted anteriorly by placing the fingers of one hand under the mandible and lifting it upward. Alternatively, the thumb may be placed behind the lower incisors while lifting the chin simultaneously (Fig. 3).

An appropriate sized oropharyngeal or nasopharyngeal airway may be inserted to maintain a patent airway.

Oropharyngeal airway: This is a semicircular plastic device which is inserted over the back of the tongue into

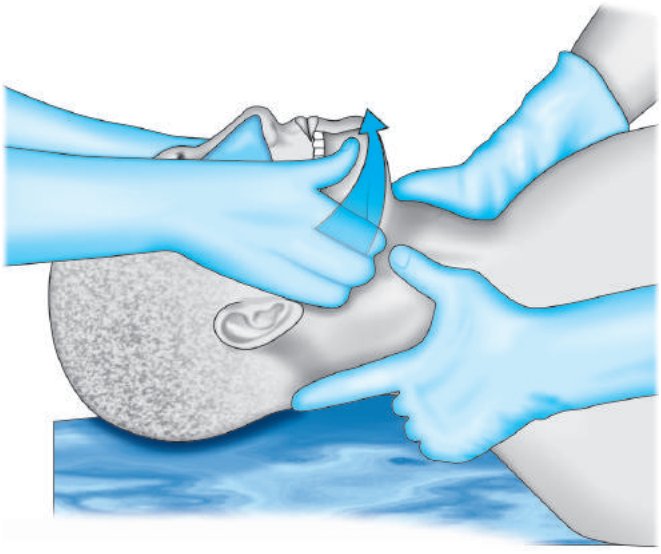


Fig. 2: Jaw-thrust maneuver.

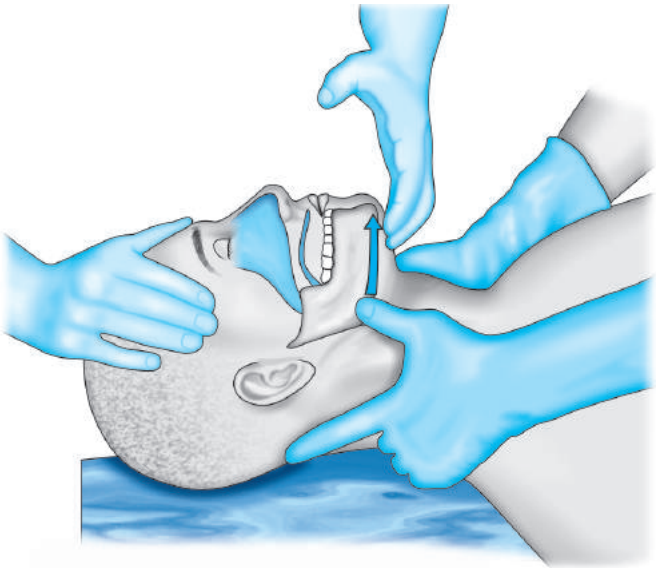


Fig. 3: Chin-lift maneuver.

by mansdocs.com

the posterior pharynx to keep the airway open. It prevents the tongue from falling back against the posterior pharynx and obstructing the airway. It also allows the suction of secretions in the oropharynx.

Nasopharyngeal airway: Nasopharyngeal airways are soft plastic devices which can be inserted in one nostril and passed gently into the posterior oropharynx. It should be well lubricated and inserted into the more patent nostril. This device should not be inserted in patients with suspected or potential cribriform plate fracture, nasal fracture or in patients with coagulopathy.

All trauma patients are assumed to be full stomach; hence it is important to anticipate vomiting and be prepared to manage the situation. Regurgitation of gastric contents in the oropharynx of patient with altered level of consciousness or obtunded reflexes poses a threat of aspiration with the patient's next breath. Hence, immediate suctioning with a wide bore cannula and rotation of the entire patient to the lateral position should be performed. All the patients with blunt multisystem injury, especially with an altered level of consciousness or a blunt injury above clavicle should be assumed to have cervical spine injury (CSI) unless proven otherwise. Hence in a trauma setting, assessment and management of patient's airway is always with cervical spine protection and great care should be taken to prevent excessive movement of the cervical spine. The patient's head and neck should not be flexed, extended or rotated while assessing or managing the airway. Appropriate immobilization devices such as semi rigid cervical collar should be used to immobilize the cervical spine and manual in line immobilization should be accomplished if there is a need to remove the anterior part of cervical collar for airway intervention. The manual in line stabilization (MILS) can be applied from the front or the side of the patient. During this maneuver, the healthcare personnel should support the occiput and mandible with both hands to maintain neck alignment without applying traction (Fig. 4). The anterior portion of the cervical collar is removed prior to laryngoscopy to allow for easy intubation, application of cricoid pressure and surgical airway if the need arises. MILS should be initiated while applying the bag and mask ventilation and as soon as the collar is removed.

Definitive airway is indicated based on following clinical findings:

- Airway problems: Inability to maintain a patent airway with impending or potential compromise of the airway.



Fig. 4: An assistant applying manual in line stabilization (MILS) to immobilize the cervical spine during laryngoscopy.

- *Breathing problems*: Adequate oxygenation is not maintained by supplemental oxygen by face mask and presence of apnea.
- *Disability problems*: TBI with Glasgow coma scale (GCS) score less than 8, requiring assisted ventilation needing protection of airway from aspiration of blood and vomitus.

One must always be prepared for the unanticipated difficult airway situation. Although the techniques used will vary according to institutional protocol and provider's experience, a difficult airway cart comprising of various size of laryngoscope blades, ETTs and bougie should always be kept ready. The standard monitoring devices used during intubation must be attached to the patient. Direct laryngoscopic guided intubation following modified rapid-sequence induction (RSI) of anesthesia accompanied with cricoid pressure and in-line cervical stabilization is the most widely practiced and safest approach to secure the airway. Anesthesia and neuromuscular blockade allow the best intubating condition and is advantageous in an uncooperative and hypoxic patient when intubation is not anticipated to be difficult. Attempts to secure the airway in an awake or lightly sedated or uncooperative patient increase the risk of airway trauma, aspiration, hypertension and laryngospasm. The induction agent and neuromuscular blocker vary in a trauma patient. Etomidate or ketamine are the preferred induction agents in case of hypovolemia. The dose of anesthetic must be decreased in the presence of hemorrhage, down to none at all in patients with life-threatening hypovolemia. Suxamethonium remains the

by mansdocs.com

neuromuscular blocker with fastest onset—less than 1 minute—and shortest duration of action of around 5–10 minutes. Administration of suxamethonium is associated with several adverse consequences. Hyperkalemia after suxamethonium administration is not seen within first 24 hours after these injuries, and suxamethonium may be used safely for acute airway management. The provider must weigh the use of suxamethonium in each individual situation. There will always be specific situations in which maintaining spontaneous ventilation during intubation is the preferred technique. Cricoid pressure should be applied continuously during emergency airway management from the time that the patient loses protective airway reflexes until endotracheal tube (ETT) placement and cuff inflation are confirmed. Although the value of cricoid pressure in occluding the esophagus has been questioned, it is simple to perform and may offer secondary benefits. Some recent evidence, however, suggests that cricoid pressure may worsen the laryngoscopic grade of view in up to 30% of patients. It is appropriate that cricoid pressure be temporarily released in case this problem is encountered.

Fiberoptic bronchoscopic guided intubation is very useful in difficult airway scenario; but in trauma setting it may have a limited role especially in ER because of the urgency for securing the airway and the presence of blood in airway which obscures visibility. Alternative airway devices include laryngeal mask airway, i-gel or esophageal-tracheal double lumen tube and the newer laryngoscopes like the glidescope, C Mac or Bullard laryngoscope which can be used in difficult airway situation. An option for urgent surgical or needle cricothyroidotomy should also be kept available.

A surgical airway (cricothyroidotomy or tracheostomy) is established when glottic oedema, laryngeal fracture or severe oropharyngeal bleed obstructs the airway and attempts to establish a patent airway by noninvasive route have failed. A surgical cricothyroidotomy is preferred over tracheostomy as it takes less time, is easier to perform and is associated with less bleeding than tracheostomy. Surgical cricothyroidotomy is achieved by making an opening in cricothyroid membrane to establish the airway. A curved hemostat may be inserted to dilate this opening and a small sized tracheal tube (5.00-7.00 mm OD) can be inserted. A cricothyroidotomy tube is replaced with a formal tracheostomy tube when the patient is able to tolerate this procedure.

Alternatively, needle cricothyroidotomy may also be done as a life saving procedure. A 12 or 14G needle is inserted through cricothyroid membrane after stabilization of trachea with the thumb and forefingers of one hand. The skin is punctured in the midline with the cannula attached to a syringe with saline filled in it. The needle is directed caudad, applying negative pressure to the syringe (Fig. 5). Once the cannula is in trachea air is aspirated in the syringe. The syringe is removed and the stylet is withdrawn, while gently advancing the catheter downward. Once the needle is in the trachea, a guide wire is passed through the needle into the trachea using the seldinger technique. The cricothyroidotomy site is dilated and cricothyroidotomy tube is advanced. It is secured in place once confirmed to be in trachea.

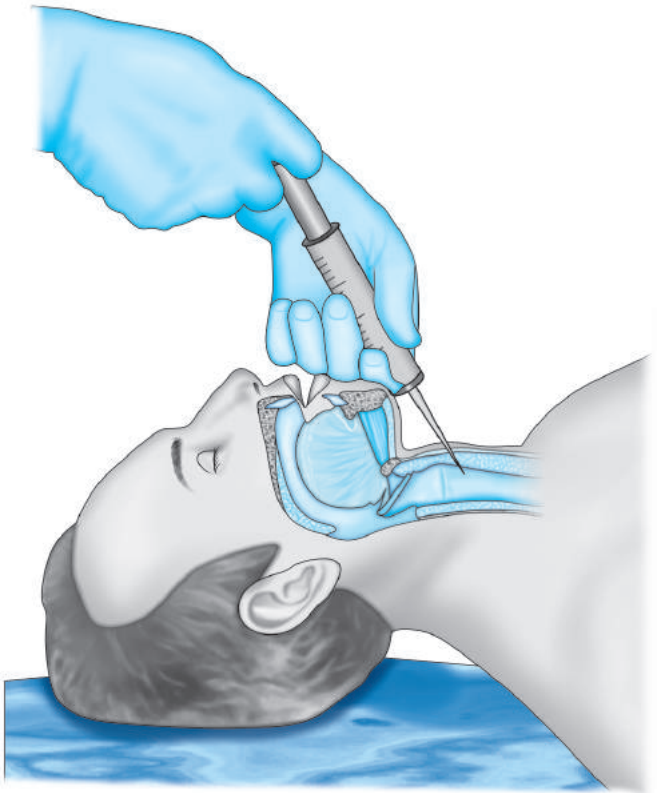


Fig. 5: Needle cricothyroidotomy.

Breathing and Ventilation

Maintaining patent airway alone is not sufficient; it is equally essential to ensure adequate ventilation. Adequate function of the chest wall, lungs and diaphragm are required for adequate ventilation, hence all the components should be evaluated. The patient's neck and chest should be exposed and inspected to examine the jugular venous distension, tracheal position and chest wall

by mansdocs.com

movement. Auscultation and percussion can also identify abnormalities which compromises ventilation. Tachypnea and decreased or absent movement of one or both hemithoraces should alert that the patient has sustained chest trauma. Asymmetrical chest movement indicates hemothorax, pneumothorax or a flail chest. The life-threatening injuries which should be identified and managed during primary survey are tension pneumothorax, flail chest with pulmonary contusion, massive hemothorax and open pneumothorax. After the airway is determined to be unobstructed, the conditions which can compromise ventilation should be addressed. Tension pneumothorax can compromise both ventilation and circulation rapidly. Needle decompression by inserting a wide bore cannula in second intercostal space in midclavicular line should be performed immediately (Fig. 6) followed by tube thoracostomy. An open pneumothorax is generally associated with soft tissue loss and should be managed by covering the wound by a sterile occlusive dressing on three sides (Fig. 7) followed by chest tube insertion. Massive hemothorax can be managed by chest drain insertion alone in majority of the patients. Any blood loss > 200 ml/hr for 2–4 hours or 1500 ml on insertion should be informed to the surgeon immediately as they are likely to need thoracotomy. Rib fractures are often missed on chest radiograph; tenderness over the fracture area during physical examination should arouse the suspicion of rib fracture. Control of pain is required to ensure adequate spontaneous ventilation. When two or more contiguous ribs are fractured at two or more places it results in flail chest and is manifested by paradoxical movement of the involved segment. Flail chest is frequently associated with pulmonary contusion resulting in hypoxemia. Flail chest with pulmonary contusion can be managed by chest tube insertion, adequate pain relief and by instituting positive pressure ventilation if indicated.

Although simple pneumothorax can compromise ventilation to less extent and can be identified during secondary survey but is of clinical relevance if patient needs emergent surgery and intubation. Positive pressure ventilation in an intubated patient with simple pneumothorax can lead to tension pneumothorax. Hence, one should ensure placement of chest drain prior to intubation and positive pressure ventilation in these cases. After intubation, the adequacy of ventilation should be assessed by auscultation and capnography. In the arterial blood gas (ABG) analysis, ventilation should be adequate in terms of oxygenation and carbon dioxide elimination.

Circulation with Hemorrhage Control

Hemorrhage that results in the reduction of circulating blood volume is the predominant cause of shock and preventable death after injury. Identifying that the patient is in shock, recognizing the source of hemorrhage, stopping the hemorrhage and volume resuscitation are the vital steps in the primary survey of these patients. The various causes of hypotension can be blood loss, tension pneumothorax, cardiac tamponade or neurogenic shock.



Fig. 6: Needle decompression for emergency management of tension pneumothorax.



Fig. 7: Three side occlusive dressing for management of open pneumothorax.

by mansdocs.com

Table 1: Gradation of shock by clinical presentation.

	Class I	*Class II*	*Class III*	*Class IV*
Blood Loss mL	Up to 750 mL	750-1500 mL	1500–2000 mL	>2000 mL
Blood Loss % Bl.vol	Up to 15 %	15-30%	30-40 %	>40%
Pulse rate	<100	>100	> 120	>140
Systolic BP	Normal	Normal	↓	↓
Pulse Pressure	Normal / ↑	↓	↓	↓
Respiratory rate	14–20	20–30	30–40	>35
Urine output (ml/hr)	>30	20–30	5–15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious & Confused	Confused & lethargic
Fluid replacement as per 3:1 rule	Crystalloids	crystalloids	Crystalloids & blood	Crystalloids & blood

Source: Permission from American College of Surgeons, Committee on Trauma Reqd.

However, once tension pneumothorax has been ruled out, one should assume that hemorrhage is the cause of shock unless proven otherwise.

Signs and symptoms of shock: The patient is assessed for signs and symptoms of shock; which mainly includes level of consciousness, color of skin, pulse rate and volume and urinary output.

Level of consciousness: Altered level of consciousness may be a sign of impaired cerebral perfusion due to reduced circulating blood volume although a conscious patient may have lost significant amount of blood.

Color of skin: Cool, clammy pale extremities with decreased capillary refill and ashen grey facial skin are helpful in establishing that the patient is in shock.

Pulse: All peripheral pulses should be palpated bilaterally for rate, rhythm and volume. A rapid, thready pulse is typically seen in hypovolemic shock. A rapid and thready pulse is indicative of hypovolemia although it could be present due to various other reasons. A patient with irregular pulse should be evaluated further to rule out cardiac injury. Absent central pulses not attributable to local causes is indicative of severe shock and requires immediate resuscitative measures to optimize cardiac output.

Urinary output: Low urine output indicates inadequate renal perfusion. Patients with less than 0.5 ml/kg/ hr urine output may be compensating for hypovolemia.

Patient may be tachypnoeic which may reflect an attempt to compensate metabolic acidosis.

Causes of shock: Hemorrhage is the most common cause of shock in a trauma patient. The source of bleeding should be determined which may be internal or external. The patient at times may have to be log rolled to rule out penetrating injuries in the back. Exsanguinating internal bleeding may occur at four sites: chest, abdomen, pelvis and long bones; as goes the following axiom "blood on the floor and four more". Clinical examination and imaging i.e. chest X-ray, pelvic X-ray or focused assessment sonography in trauma (FAST) usually identifies the source of bleeding. The non-hemorrhagic causes of shock are mainly cardiogenic, obstructive, neurogenic or septic if the patient presents late after injury.

Severity of shock: Hemorrhage can be graded into four classes according to the ATLS based on clinical signs and are helpful in estimating the amount of blood lost (Table 1).

Class I hemorrhage: The patient with less than 15% blood volume loss, i.e. around 750 ml in a 70 kg adult is categorized as Class I shock. The patient usually does not present with any signs and symptoms except for anxiety.

Class II hemorrhage: A patient with 15–30% blood volume loss, i.e. around 1500 ml is categorized as Class II shock. The patient may be mildly anxious, slightly tachycardic, tachypnoeic and also have decreased pulse pressure. There is minimal change in systolic blood pressure and the urinary output is mildly affected.

Class III hemorrhage: Ongoing blood loss of around 1500–2000 mL, i.e. 30–40% of blood volume causes Class III shock. The patient with Class III shock presents with anxiety, increased tachycardia, tachypnea, altered consciousness, decreased capillary refill and decreased urinary output.

by mansdocs.com

Table 2: Response to fluid resuscitation.

	Rapid response	*Transient response*	*Minimal or no response*
Vital signs	Return to normal	Transient improvement, recurrence of decreased blood pressure and increased heart rate	Remain abnormal
Estimated blood loss	Minimal (10–20%)	Moderate and ongoing (20–40%)	Severe (>40%)
Need for more crystalloid	Low	High	High
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and crossmatch	Type-specific	Emergency blood release
Need for operative intervention	Possibly	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

Source: Permission from American College of Surgeons, Committee on Trauma Reqd.

Class IV hemorrhage: Bleeding of more than 2000 ml causes Class IV shock and the patients present with drop in systolic blood pressure with narrow pulse pressure, tachycardia, tachypnea, decreased capillary refill, decreased level of unconsciousness and minimal or absent urine output.

Resuscitation should be started simultaneously with control of bleeding. Two wide bore, short peripheral IV cannula should be secured to administer fluids. Blood sample should be sent for grouping and cross matching and baseline hematocrit studies. Blood gases and/or serum lactate levels should be done to assess the presence and degree of shock. Initial resuscitation in a trauma patient involves administering 1–2 liter of warm crystalloid infusion. Current recommendations emphasize maintenance of deliberate hypotension during active bleeding by restricting crystalloid infusion and instituting early transfusion of red blood cells, plasma, and platelets for correcting blood loss. Clinical manifestations of coagulopathic disorder should be treated empirically with blood and blood products as per the institution massive transfusion protocol (MTP). The most widely followed protocol which has shown to improve survival in few studies is 1:1:1 ratio of red cells, fresh frozen plasma and platelet. Direct, firm pressure can be applied over the bleeding area or the involved artery at the site that is proximal to the wound. Most bleeding can be stopped or at least temporarily controlled by application of direct pressure. A firm pressure dressing and elevation of the bleeding area can also help in decreasing the bleeding till surgical control is achieved. Blind clamping of bleeding vessels should be avoided to prevent injury to adjacent structures (e.g. nerves). Tourniquet may be applied to stop life-threatening bleeding in cases of amputation injuries or open extremity, when other measures have failed to control bleeding. However, it must be released periodically to avoid prolonged ischemia and tissue necrosis. Management of internal bleeding includes chest decompression, pelvic binder, splint application, surgical intervention or interventional radiologic procedure to control hemorrhage.

According to the response to the fluid resuscitation there are three categories of patient as described in Table 2. First category involves those who respond rapidly. The other two categories which include transient responders and the non-responders are probable candidates for immediate surgical control of bleeding.

Disability

Rapid neurologic assessment is performed during primary survey which mainly includes patient's level of consciousness, pupillary size and reaction and spinal cord injury level. GCS is a quick and simple method for assessing the neurologic status of a patient and predict his outcome. The GCS scoring is done by assessing the motor response, verbal response and eye opening and can be used as a measure to grade the severity of brain injury (Table 3). A patient with GCS score of 13–15 is categorized as mild head injury, whereas GCS score of 9–12 is designated as moderate head injury. A GCS score of 8 or less is severe head injury and is generally accepted as coma. GCS scoring should be done early to prevent secondary brain injury, and provide a baseline score for further trends. Best motor response in GCS is the most predictive of neurologic outcome. Pupils should be examined for size, reactivity, and symmetry; and sensory or motor loss in each of the extremities should be determined. Immediate CT Head should be done if significant abnormalities on neurologic examination are present. However, altered level of consciousness also requires

by mansdocs.com

Table 3: Glasgow coma scale scoring.

Score	*Eye opening*	*Best verbal response*	*Best motor response*
6			Obeys commands
5		Oriented	Localizes pain
4	Spontaneous	Confused	Flexed to pain
3	To speech	Inappropriate words	Flexion of arms with ext of legs (decorticate)
2	To pain	Incomprehensible sounds	Extension
1	None	No verbalization	None

Source: Permission from American College of Surgeons, Committee on Trauma Reqd.

re-evaluation of oxygenation, ventilation and tissue perfusion. Hypoglycemia and influence of drugs must be ruled out as cause of altered sensorium. Most of trauma patients with a diminished GCS score will have non-operative causes contributing to altered sensorium. But those few who require evacuation of an epidural or subdural hematoma, timely intervention by surgery influences outcome to a great extent.

Cerebral blood flow (CBF) is usually autoregulated by vasodilation and vasoconstriction, which allows for constancy over a wide range of blood pressures. This autoregulatory compensatory mechanism is disrupted by TBI. Intracranial hemorrhage causes a mass effect which is initially compensated by venous constriction and absorption of cerebrospinal fluid (CSF). However, since skull is a closed space and as the compensatory mechanisms begin to fail, CBF reduces. Intracranial pressure (ICP) and mean arterial pressure (MAP) are the important determinants of CBF. Normal ICP is 10 mm Hg; sustained increased ICP (> 20 mm Hg) can decrease the brain function and outcome. Similarly hypotension can affect the CBF. All measures should be taken to prevent secondary brain injury in a head injured patient by maintaining adequate circulatory blood volume (systolic blood pressure > 90 mm Hg), adequate oxygenation and ventilation, normothermia and normal blood sugar levels. Early surgical stabilization of patients with unstable spinal canal injuries and incomplete neurologic deficits is also beneficial.

Exposure and Environmental Control

A thorough examination and assessment of the patient is performed by completely undressing the patient or cutting his garments. Body temperature may fall with exposure of the patient, cold resuscitation fluids and loss of normal temperature regulating reflexes. Hypothermia, defined as a core body temperature below 35°C, is associated with acidosis, hypotension and coagulopathy in severely injured patients. In a retrospective study with patients, hypothermia was an ominous clinical sign, accompanied with high mortality and blood loss. The profound clinical effects of hypothermia ultimately led to higher morbidity and mortality, and hypothermic patients required more blood products as compared to normothermic patients. Hence, hypothermia should be prevented throughout the resuscitation period. Once the patient has been assessed, he should be covered with warm blankets to prevent hypothermia. Warm intravenous fluids should be administered and a warm environment should be maintained.

Adjuncts to Primary Survey and Resuscitation

The adjuncts which are used during primary survey include:

1. *ECG monitoring*: ECG monitoring should be done in all patients. Tachycardia, bradycardia, dysrythmia, ST segment changes should be monitored.
2. *Urinary catheter*: Urine output is a sensitive indicator of adequacy of resuscitation as it reflects patient's volume status and renal perfusion. Urinary catheter should be inserted in trauma patients whenever indicated. Transurethral catheter insertion is contraindicated in patients with a possible urethral injury, which should be suspected in the presence of blood at urethral meatus, perineal echymosis or high riding prostate.
3. *Gastric catheter*: A gastric catheter should be inserted to decompress the stomach and hence decrease the risk of aspiration and also to assess for upper gastrointestinal hemorrhage.
4. Other monitoring such as pulse rate, blood pressure, oxygen saturation, respiratory rate, body temperature, ABG and serum lactate levels should be monitored continuously.

by mansdocs.com

5. Radiologic examination and diagnostic studies during primary survey. Chest X-ray and pelvic X-ray are the two adjuncts which are done to provide information and guide resuscitation efforts of patients with blunt trauma. FAST and diagnostic peritoneal lavage (DPL) are useful tools to detect occult intraabdominal bleed. Identification of the source of bleeding may indicate whether operative control of hemorrhage is indicated.

SECONDARY SURVEY

With the resuscitation underway after the primary survey has been completed, and the vital functions coming back to normal, the focus shifts to secondary survey. This includes detailed examination of the patient to identify all the injuries from head to toe, front and back and reassessment of all vital signs. It also includes a complete history, laboratory studies and radiological evaluation. Each region of the body is completely examined and any injury missed in earlier assessments is diagnosed and managed accordingly. A complete neurologic examination including a repeat GCS score determination is performed during the secondary survey. Diagnostic studies and interventions are performed depending on the findings of secondary survey.

Patient's history should include the mechanism of injury, previous medical illness, current medications, allergies and tetanus immunization. AMPLE mnemonic is useful for this purpose, i.e. Allergies, Medications currently used, Past illness/Pregnancy, Last meal and Events/Environment related to the injury. If mechanism of injury cannot be obtained from patient, then family person or attendant should be consulted. Mechanism of injury has a great bearing on the pattern of injury. The direction and force of injury helps in prediction of injuries. Injuries may be blunt or penetrating and thermal, chemical or radiation injury may also be involved. Physical examination from head to toe should exclude occult injuries. Laceration or contusion or evidence of fracture on scalp and other parts of the body should be ruled out. Racoon eyes (periorbital hematoma) and battles ear (retroauricular hematoma) signify underlying basilar skull fracture. Nasogastric tube should not be placed in patients with nasal bone fracture or fracture of base of skull. Airway injury, burn patients and maxillofacial injury patients may require elective intubation. Chest, abdomen, perineal area, rectum and extremities should be systematically examined. Patient should be log rolled to examine the back for spine injury (*see* Fig. 5). Per rectal examination is also performed at this time. Logrolling also gives an opportunity to remove the spine board. The spine board must be removed as soon as possible once the patient has been transferred on a firm trolley, as prolonged use can lead to pressure ulcers.

Laboratory studies should be minimal which includes complete blood count, electrolytes and blood glucose level. In patients with evidence of hypovolemia, blood grouping, renal function tests and coagulation profile should be done. Other blood tests vary according to the type of injury like the liver function tests and serum amylase level. ABG analysis should be done to confirm the adequacy of ventilation and metabolic balance.

Radiological evaluation is done as the primary survey is being carried out. In case of head injury, computed tomographic scanning (CT scan) is essential. CT scan of spine is often helpful to rule out CSI. CT scan of chest and abdomen is done in multiple blunt trauma cases or as required by injury pattern. Whole spine injury may be ruled out in these scans. Chest radiographs in upright position may be done to look for pneumothorax, hemothorax, mediastinal widening, and fractures and to confirm tube position. FAST is done as screening method for blood in abdomen or pericardial cavity. In equivocal cases or when patient is stable, CT scan of abdomen is confirmatory. Cystogram or urethrogram may be required if bladder or urethral injury is suspected. Radiograph of extremities should be done on basis of physical examination.

TERTIARY ASSESSMENT AND ONGOING PHYSIOLOGIC SYSTEM CONTROL

When a patient arrives in the ICU, the primary and secondary survey will have been completed, however it is essential to repeat the primary and secondary survey on admission to ICU as 10% of injuries may have been missed during initial assessment. Further assessment at this time called tertiary survey should also be performed.

It includes:

- Reviewing the anatomical injuries and physiologic disturbances
- Re-examine the patient for missed injuries and new complications
- Review the imaging
- Perform a more detailed assessment with clinical evaluation supplemented with intensive care monitoring.

by mansdocs.com

The aim is to identify and treat physiologic derangements which extend beyond the ABCDE approach and mainly include:

- Respiration
- Circulation
- Nervous system
- Analgesia and sedation
- Metabolic control
- Nutrition
- Host defense
- Abdominal issues
- Musculoskeletal system

When handing over information to the ICU team, a systematic approach, i.e. ABCDE approach should be followed. It is a time when miscommunication can occur and important information can be missed. Handing over the patient is an opportunity to summarize the information of the relevant findings, diagnostic studies, intervention taken and physiologic status of the patient.

Respiratory Control

Patency of the airway must always be confirmed on receiving the patient, even if an ETT is in place. All tubes can get displaced during transportation. ETT cuff should be checked for adequate cuff inflation and reinflated in case of any air leak around the cuff. The chest should be reexamined for evidence of hemopneumothorax. In case of any secretions in the ETT, gentle suction should be performed. Close suction catheter may be inserted for intermittent suction. The chest drain position at the skin level and the fluid column in the underwater seal bottle should be assessed and documented. If the chest drain bubbles excessively, it should be notified to the treating surgeon/intensivisit as it could indicate tracheobronchial injury. Delayed onset of pneumothorax or hemothorax may follow chest trauma. Monitoring of the chest tube drainage fluid is essential. Any amount more than 200 ml for 2–4 hours should be immediately informed to the surgical team. An abrupt decrease in high volume chest tube output should raise the suspicion of blocked tube or caked hemothorax. Chest tube removal algorithms should be followed which include lung expansion, resolution of pneumothorax or air leak and drainage less than 2 ml/kg/day. Chest drain tube should be removed at maximal deep inspiration. X-ray chest is recommended after chest tube removal to rule out recollection of blood or fluid or recurrence of pneumothorax; which may occur in 6–8% of patients. Pulmonary contusions and resulting adult respiratory distress syndrome (ARDS) may manifest on second or third day after injury. Hence, close monitoring of these patients is essential and any decrease in oxygen saturation or clinical deterioration should be looked for.

Circulatory Control

Trends in the heart rate, blood pressure, urine output, hemoglobin level, serum lactate and base deficit helps to detect unrecognized hemorrhage. Central venous pressure (CVP) measurements may be used to identify decreased intravascular volume status, although its value has been disputed. However, it may be used to guide fluid resuscitation in ICU. If the circulatory monitoring suggests continuous bleeding, the source of bleeding must be identified and managed accordingly.

Accepting a lower blood pressure up to 90 mm Hg systolic and limiting fluid infusion may be appropriate till bleeding has been controlled. The source of bleeding mentioned in the primary survey should again be looked for. All the iatrogenic causes of hypotension such as oversedation or epidural anesthetic infusion should also be ruled out.

Other non-hemorrhagic causes of hypotension should also be assessed for, which includes:

- Cardiac tamponade
- Cardiac contusion
- High CSI
- Brainstem compression
- Septic shock
- Drug or fluid allergy or blood reaction

The risk of bleeding from organs such as liver and spleen remains high for several days after injury. Bleeding may resume when blood clots get dislodged or are broken down. The patient must be kept under observation for several days.

Hemoglobin (Hb): It is important to maintain adequate Hb concentration. However, blood transfusion is not devoid of risks and complications. However, blood transfusion is not devoid of risks and complications. Hence, prior to the control of bleeding, blood and blood product should be transfused to maintain a Hb of 10 gm%. Once the bleeding has been controlled, a target Hb level of 7–8 gm% is appropriate in most patients.

Hemostasis: Dilutional coagulopathy and hypothermia are the commonest contributory factory of coagulopathy

by mansdocs.com

in severely injured patients. Laboratory results such as international normalized ratio (INR) active prothrombin time (APTT), fibrinogen level and platelet count helps to identify the problem and guide transfusion therapy. However, in a patient needing rapid transfusion, in the face of ongoing blood loss, the situation is urgent and justifies empirical treatment with blood and blood products without waiting for laboratory results. Each institution should have its own massive blood transfusion protocol.

It is also important to monitor the body temperature and serum ionized calcium levels as hypothermia and hypocalcemia are easily correctable factors in impaired hemostasis. Even minor clotting abnormalities should be corrected vigorously in injuries such as significant hemorrhagic cerebral contusion or a contained hepatic or splenic hematoma even if there is no clinical evidence of active bleeding. A balance between the risks of precipitating further bleeding against the risk of venous thromboembolism (VTE) needs to be maintained in patients with hemorrhagic cerebral contusions, contained abdominal hematomas or major pelvic hematomas. Thromboprophylaxis should be initialed as soon as possible if no contraindication exists. Mechanical compression devices may be used from the outset if there is no lower extremity injury.

Nervous System Control

The goals for the patient with TBI include maintaining a patent airway, maintain adequate oxygenation and ventilation, maintaining cerebral perfusion through reduction in ICP and maintaining systolic blood pressure more than 100 mm Hg, restoration of fluid balance, infection control and detecting and managing complication.

A head injured patient needs continuous monitoring of the neurologic status. This is best done by using the internationally accepted means, i.e. GCS score. A fall of more than 2 points in the GCS and an absolute value of 8 or less is a matter of concern and needs to be evaluated further. Serial CT scans of the head, preferably with mobile CT machine should be done in case of signs of any clinical deterioration.

Any clinical sign of raised ICP which includes a slow pulse rate and a high blood pressure, i.e. Cushing reflex should be monitored in patients with TBI. A dilated pupil on the ipsilateral side of the injury indicates expanding intracranial and urgent intervention.

Many patients would be with the ICP monitor in a busy Neurotrauma ICU. Although the device is inserted by a trained neurosurgeon, the care of the device, monitoring and notification of raised ICP is in the critical care unit staff's domain.

Monitoring ICP

The purpose of ICP monitoring are to identify elevation of ICP early in its course (prior to cerebral damage occurs), to quantify the degree of elevation, to initiate appropriate treatment and also to evaluate the effectiveness of treatment. ICP can be monitored with the use of an intraventricular catheter (ventriculostomy), intraparenchymal catheter, an epidural or subdural catheter or bolt (Fig. 8). When a ventriculostomy drain is used for ICP, a fine bore catheter is inserted into a lateral ventricle. The catheter is connected to a transducer by a fluid filled system and the pressure is recorded in the form of an electrical impulse. The ventriculostomy catheter not only monitors the ICP, but also allows CSF drainage, particularly during acute increases in pressure. Continuous CSF drainage under pressure control is an effective technique of controlling intracranial hypertension (ICH). Strict aseptic precautions should be maintained while handling any part of the ICP monitoring system. The site of insertion should be closely monitored to detect early signs of systemic infection. Any leakage around any connection or stop cock should be checked since even small leak can give erroneous pressure recordings and cause infection.

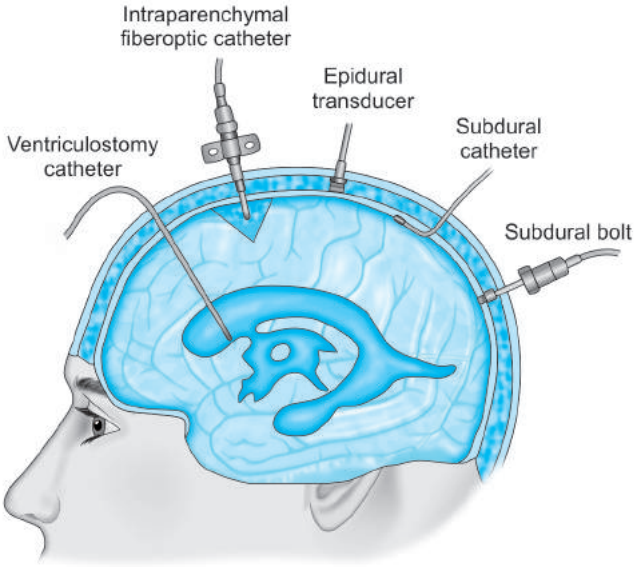


Fig. 8: Various different techniques of ICP monitoring.

by mansdocs.com

When ICP is monitored with a fluid filled system, the zero calibration is done at a reference point, i.e. 2.5 cm above the ear. This point corresponds to the level of foramen of Monro. The patient's position changes the CSF pressure readings, hence for subsequent pressure readings, the head should be in the same position relative to the transducer. Proper patient positioning helps in reducing ICP. Elevation of the head at 30–45 degrees promotes venous drainage and should be maintained unless contraindicated. Extreme rotation and flexion of neck should be avoided as it can increase ICP by causing compression of the jugular veins. ICP can be significantly affected by relatively minor changes in position or intervention.

Spacing of interventions likely to cause rise in ICP may help in preventing increase in ICP. The ICP should not be more than 25 mm Hg during nursing interventions and should return to baseline within 5 minutes. ETT suctioning can increase the ICP significantly. Hence, the patient should be preoxygenated with 100% oxygen prior to suctioning and briefly hyperventilated on the ventilator. Patients with potential for significant increase in ICP should be well sedated before initiation of any nursing intervention.

Care of Postoperative Neurotrauma Patient

Close monitoring for any deterioration is required in patients who have undergone surgery for TBI. Even a small degree of hypoxia can increase cerebral ischemia; hence it is essential to assess respiratory function in these patients. Frequent neurologic checks should be done as a change in level of consciousness or response to stimuli may be the first sign of increasing ICP, which could be a result of cerebral edema or bleeding.

The surgical dressing should be examined for any soakage with blood and/or CSF. Any sign of infection at the incision site should be monitored which can present with tenderness, swelling, would dehiscence or foul odor. Seizures are potential complications in these patients and it should be carefully recorded and reported. All precautions should be taken to prevent any injury to the patient during seizure activity.

Analgesia and Sedation

A multiply injured patient who is being mechanically ventilated may be in severe pain and may be restless. Analgesia should be provided depending on the injuries sustained and the patient's response to its administration. Opiod infusion may be used to relieve pain; being standard practice in majority of ICUs. Epidural catheter may be inserted for pain relief in patients with multiple rib fracture. Coagulopathy and spinal cord injury must be excluded prior to epidural catheter insertion. A propofol or benzodiazepine may be used in conjunction with opioid analgesia in ventilated trauma patient in the ICU. Sedation should be used judiciously in a patient with TBI, as an awake non-sedated patient is required to assess the neurologic status. However, when the ICP is raised, good sedation and analgesia are key measures for controlling it.

Metabolic Control

Renal function: Maintenance of renal perfusion and renal function is a major concern following severe trauma. In general, urine output should be maintained more than 0.5 mL/kg/hr in adults and above 2 mL/kg/hr in children. Hypovolemia is the most likely cause of oliguria; hence adequate fluid resuscitation guided by clinical status and CVP is recommended to prevent renal failure. Other causes of reduced cardiac output; myocardial contusion or infarction, cardiac tamponade and injury to the kidneys due to rhabdomyolysis or radiological contrast should also be ruled out in patients with oliguria.

In case of acute anuria, the urinary catheter should be checked for obstruction especially in patients with significant hematuria. In patients with TBI, diabetes inspidus may cause a urinary output of more than 300 mL/hr, which if untreated will result in rapidly progressive hypernatremia and hypovolemia. Hence, any increase in the urine output should be addressed early so that it can be evaluated further and managed accordingly. It is important to remember that previous treatment with mannitol and hyperglycemia can also cause high urine output.

Nutrition

Feeding should be started as early as possible, preferably by enteral route, rather than parenteral route. Parenteral nutrition may be indicated in direct injury to the gastrointestinal tract, retroperitoneum injury, abdominal compartment syndrome (ACS) and hypokalemia, all of which may cause paralytic ileus. It is essential to fulfill the caloric demands of a trauma patient as the nutritional demand increases in trauma patients. Close communication between intensivist, surgeon, dietician and nursing staff is essential to guide, administer and monitor the nutrient and caloric intake.

by mansdocs.com

Host Defense

Trauma patients are prone to infection due to primary contamination of wounds or nosocomial infection due to multidrug resistant hospital organisms. Prompt and thorough surgical debridement of the wound and care of the wound thereafter is of utmost importance to prevent infection. Several key factors contribute to secondary infections:

- Poor hospital hygiene (especially inadequate hand washing)
- Presence of vascular lines, drains and tubes
- Presence of resistant organisms due to inappropriate (i.e. long term or inappropriately broad spectrum) antibiotic usage
- Immunosuppression as a consequence of severe trauma
- Poor gut perfusion allowing translocation of bacteria into circulation.

Simple measures taken by the nursing staff can significantly contribute in decreasing infection. Hand hygiene remains one of the most important and well proven methods of decreasing infections. All tubes, drains and lines should be removed with aseptic precautions as soon as they are no longer required.

Early initiation of enteral feeding also helps in preventing infection. It is easy to overlook the need for tetanus prophylaxis in the hustle of trauma resuscitation and should be administered in ICU if not given in ER. Human tetanus Ig may be needed in contaminated wounds, especially if the patient's immunization status is incomplete or unknown.

Abdominal Problems

A critical car physician will encounter patients in ICU, who have undergone "damage control surgery". Major hepatic and abdominal vascular injuries often require "damage control approach"; wherein critically injured hemodynamically unstable patient is brought to the ICU postoperatively for further stabilization and management. These patients often arrive in the ICU with hypothermia, acidosis and coagulopathy.

The goals of management in ICU after damage control surgery are to rewarm the patient with warm blankets and warm IV fluids, correct acidosis by restoring intravascular volume and organ perfusion and correction of coagulopathy by blood and blood component therapy. The treating staff should have high degree of suspicion for rebleeding; which may require urgent re-exploration in 20% of these patients. In majority of cases of 'damage control' the abdomen is left open with plans to return to OR in 24–48 hours and definitive closure being performed at later date. In most circumstances temporary closure of the open abdomen is achieved by covering with "Bogota bag" or "Vac Pack" (negative pressure dressing).

A frequently missed condition in trauma critical care setting is intra-abdominal hypertension (IAH) leading to ACS. IAH is the pathologic elevation of IAP and is defined as sustained or repeated IAP >12 mm Hg. ACS is defined as sustained IAP >20 mm Hg associated with new onset organ dysfunction or future. This condition occurs when there is an increase in intra-abdominal pressure (IAP) due to intraperitoneal or retroperitoneal hemorrhage, ascitic fluid accumulation, edema secondary to massive fluid resuscitation or intraoperative surgical closure of the abdomen under tension. IAH and ACS are potentially life threatening complications with deleterious effects of elevated pressures on multiple organs. IAH decreases cardiac output by compressing the aorta and decreasing the venous return. The cephalad displacement of both hemidiaphragms by increased IAP results in decreased chest volume and lung compliance leading to hypoxia. Decreased volume within the pleural cavity predisposes to atelactasis and infection contributing to further hypoxia. Ventilated patients with IAH require increased airway pressure to deliver a fixed tidal volume. Vascular compression can decrease blood flow to the liver and kidneys with resultant dysfunction. IAH can also decrease ICP significantly.

IAP monitoring should be done in patients who are at high risk for developing IAH. The gold standard method for monitoring IAP is by measuring pressure via a urinary catheter within the bladder. IAP can be measured by commercially available kits.

Medical management includes nursing the patient in supine position, decompression of stomach by continuous nasogastric drainage, adequate pain control and sedation. Neuromuscular relaxants .may be required on rare occasions. Surgical decompression is indicated if the patient is unresponsive to conservative therapy.

Musculoskeletal Trauma

A patient, who has sustained musculoskeletal trauma in isolation or concomitant with other injuries, should be

by mansdocs.com

monitored for the development of early complications such as shock, fat embolism syndrome, compartment syndrome and other complications like VTE and infection. Hypovolemic shock resulting from hemorrhage is more frequently noticed in trauma patients with pelvic fractures. Stabilizing the fracture to prevent further bleeding, blood and blood product transfusion, adequate analgesia and providing proper immobilization are the basic principles of managing this situation. Fat embolism syndrome (FES) may develop after fracture of long bones or pelvic bones or crush injuries. Subtle personality changes, restlessness, irritability or confusion in a patient with long bone fracture should alert the nurse as they all could be early manifestations of FES. Immediate ABG analysis and supportive care is indicated. A swollen and tense extremity should be monitored closely for the development of a compartment syndrome, particularly in patients with altered sensorium. Serial frequent assessment of neurovascular function is essential and focuses on the "five Ps" i.e. pain, pallor, pulselessness, paresthesia and/or paralysis. Loss of pulse is a very late finding. A hallmark sign of compartment syndrome is severe throbbing pain, which continues to increase despite opioid administration and seems out of proportion to the injury. Severe pain on passive stretch of the involved muscle group is also an early suggestive sign of compartment syndrome.

In an uncooperative patient or when examination is unreliable, compartment pressure may be monitored using a needle with a standard gauge pressures more than 30 mm Hg warrants prompt treatment. The surgeon needs to be notified immediately if neurovascular compromise is suspected as any delay in treatment in treatment may result in permanent nerve and muscle damage or even necrosis and amputation. The affected extremity is maintained at the heart level and the cast or plaster is opened to relieve some pressure. If conservative measures do not restore tissue perfusion and relieve pain within one hour, urgent fasciotomy is indicated.

Close monitoring of the patient for VTE is also essential as patients with fracture of lower extremities and pelvis are at high risk for developing this complication. Prevention of VTE either by pharmacologic thromboprophylaxis and/or use of mechanical devices should be practiced. Any sign of infection in patient with musculoskeletal injury should be notified to the orthopedic surgeon and treated appropriately.

REHABILITATION

Rehabilitation is a crucial component of trauma care which should start in the ICU and continue for as long as it is beneficial after discharge from ICU. Once the medical condition is stabilized, collaborative efforts of the occupational therapist, trauma physician, intensivist and nursing staff is required to maximize the functional interdependence of the patient. It is essential to identify patient's functional deficits and disability and provide physical and occupational therapy and psychological support to the patient. Interventions which should be taken by nursing staff with other team members includes passive joint range of motion, isometric strengthening, speech therapy, ambulating with assistive devices and prevention of bed sores.

BRAIN DEATH AND ORGAN DONATION

A large percentage of brain dead patients are represented by trauma patients in a trauma ICU. They contribute to a large pool of potential organ donors. There is a wide gap between the number of organs available for transplantation and the number of patients needing organ transplant. The major reasons for this being relatives not consenting for organ retrieval of their near and dear ones.the consent rate can be increased by making the family understand the concept of brain death and the benefits which other patients would get after receiving the organ. This would require exhaustive counseling of the near relatives by the organ procurement team. The critical care team plays a vital role in this whole process by not only being compassionate towards the relative and counseling them but also by maintaining adequate organ perfusion till the organs are retrieved.

SUMMARY

Trauma is one of the leading causes of mortality worldwide. Trauma critical care is a specialized discipline with expertise in managing these patients. Trauma care includes primary survey with simultaneous resuscitation, secondary survey, definitive care and tertiary survey. Continuum of care is provided in ICU; trauma critical care physician playing an important role. The aim of management in ICU is to identify and treat physiologic derangements in various organ systems. ICU team also has a crucial role to play in rehabilitation of the patient.

by mansdocs.com

BIBLIOGRAPHY

1. American College of Surgeons. Advanced trauma life support, 9th ed. Chicago; 2012.
2. ASA Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies. An updated report by the American Society of Anesthesiologists task force on perioperative blood transfusion and adjuvant therapies. Anesthesiology. 2006;105:198-208.
3. CRASH-2 collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploraanalysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377(9771): 1096-1101, 1101.e1 -2.
4. Dutton RP. Resucitative strategies to maintain homeostasis during damage control surgery. Br J Surg. 2012;99(1):21-28.
5. Fink MP, Abraham E, Vincent JL, Kochanek PM. Textbook of Critical Care, 5th ed. Philadelphia: WB Saunders; 2005.
6. Guidelines for the management of severe traumatic brain injury, 3rd edn. A joint project of the Brain Trauma Foundation, American Association of Neurological Surgeons and Congress of Neurological Surgeons. J of Neurotrauma. 2007;24.
7. Napolitano L. Resuscitation end points in trauma. TATM. 2005;6(4):6-14.
8. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: An updated European guideline. Crit Care. 2013;17(2):R76.
9. Tobin JM, Varon AJ. Review article: update in trauma anesthesiology: perioperative resuscitation management. Anesth Analg. 2012;115(6):1326-33.

by mansdocs.com

CHAPTER

38

Management of Spinal Injury

Samir Sahu

INTRODUCTION

Spinal cord injury (SCI) is devastating for the patient and family. They cause immense physical, psychological and functional disability. The cost to the patient and the society due to hospitalization, rehabilitation and ongoing care and loss of productivity are enormous.

ETIOLOGY

Spinal cord injury are mainly due to motor vehicle accidents, falls and sports injuries. About 2% of all blunt trauma patients will have sustained a SCI, and these rates are higher in the setting of severe closed head injury. Cervical SCI accounts for 38% of them, mostly at the C4–5 level. 52% of SCI are complete and around 34% have associated significant head or chest injuries. Patients with acute SCI are at risk of neurologic deterioration due to secondary injury to the spinal cord. A potential cause of secondary injury is through inadvertent manipulation of the spinal cord in the setting of an unstable spinal column injury.

PATHOGENESIS

Trauma to the spinal cord results in immediate primary and delayed secondary injury.

Primary Injury

Direct mechanical injury may produce focal compression, laceration or traction injury to the cord. Transection is unusual and ischemic injury may occur.

Secondary Injury

Local hypoperfusion and ischemia begin at the site of injury and extend progressively over hours from the site of injury in both directions. There is loss of spinal cord autoregulation along with hypotension in high SCI. Apart from ischemia-free radicals, eicosanoids, calcium, proteases, phospholipases and excitotoxic neurotransmitters contribute to secondary injury.

Petechial hemorrhages begin in gray matter, progress over hours and may result in significant hemorrhage in the cord. Edema in the cord may ultimately lead to neuronal necrosis. In the white matter, vasogenic edema, axonal degeneration and demyelination follow. Infiltration of polymorphs occurs in hemorrhagic areas leading to coagulative necrosis and cavitation.

CLINICAL FEATURES

Spinal and spinal cord injuries should be suspected after severe trauma or head injuries if there are motor or sensory symptoms or signs, or the patient reports neck or back pain. The posterior column from occiput to sacrum is readily accessible to the clinician in a patient who is log rolled with in-line stabilization of the cervical spine. A careful search for localized tenderness, bruising and a gap or step is essential.

Neurological Assessment

A detailed neurological examination is essential. This includes motor and sensory function, reflexes as well as

by mansdocs.com

anal function. The vital capacity should be measured. Examination may be difficult due to head or other injuries, pain, alcohol or administration of analgesics and other drugs.

In an alert patient, SCI may be obvious with muscle paralysis or weakness, numbness and absence of reflexes. In a complete SCI, there is muscle paralysis with a sensory loss below the level of injury. Spinal shock with muscle flaccidity, absence of reflexes and vaso-/venodilatation, loss of bladder function and paralytic ileus may be present.

Associated Injuries

Injuries of the spinal column are always associated with significant energy application to the patient and on this basis, as per Advanced Trauma Life Support (ATLS) protocols, careful and repeated search for non-spinal, visceral and other skeletal injuries should be carried out. Up to 20% of spinal injuries occur at multiple levels and there is evidence that in the upper cervical spine one identified injury is associated with an 80% chance of a second injury in the cervical spine. The assessing clinician should therefore assume a second injury, and all patients with a significantly identified skeletal injury in the spinal column should have the whole spinal column examined clinically and assessed radiologically either with plain X-rays from occiput to sacrum or with rapid sequence multidetector computerized tomography (CT). This protocol should also be adopted in the unconscious polytraumatized patient where a clinical assessment is unreliable. The experienced spinal clinician should be establishing treatment priorities during the assessment process so that at the end of this process not only are the skeletal, neurological and associated injury are quantified but also an outline treatment plan has been completed. American Spinal Injury Association (ASIA) Impairment Scale provides a good classification for the initial as well as recovery grading in spinal injuries (Table 1).

Table 1: American Spinal Injury Association (ASIA) Impairment Scale.

A	Complete:	No sensory or motor function is preserved in the sacral segments S4-S5.
B	Incomplete:	Sensory but not motor function is preserved below the neurological level and includes sacral segments S4-S5
C	Incomplete:	Motor function is preserved below the neurological level and more than half of the key muscles below the neurological level have a muscle grade less than 3
D	Incomplete:	Motor function is preserved below the neurological level and at least half of the key muscles below the neurological level have a muscle grade greater or equal to 3
E	Normal:	Sensory and motor function is normal

IMAGING

X-Ray

Plain X-rays remain the primary screening method for SCI. Views of the entire cervical column from the base of the skull till T1 are adequate. The three-view series consisting of lateral, anteroposterior and odontoid (open mouth) views are standard. Lesions may not be seen if the views are inadequate or of poor technical quality or the observer is inexperienced. The anterior column is clearly visualized in plain X-rays. The increased use of the two-column model for describing injuries to the spinal column rather than the previously used three-column model, has simplified the process of classification and also focuses the clinician on assessing, using all possible modalities, both the anterior and the posterior columns.

Computerized Tomography

The sensitivity of CT scanning is much greater than plain X-rays especially with the newer multidetector CT machines. CT scanning has an essential role in the detection and evaluation of spinal injuries as well as exclusion of injuries for spinal clearance. The anterior column is clearly visualized in all modalities of CT scanning. Two-dimensional CT reconstruction helps in identifying type B fractures and in combination with three-dimensional reconstruction gives a better visualization of some fracture patterns in the anterior column. Two-dimensional CT reconstruction is a powerful modality for identifying injuries in the posterior column. CT scanning should be done in all suspected or proven spinal injuries. If patients are unconscious or have suffered severe or multiple trauma, CT scanning should be undertaken as the first line imaging without screening plain X-rays.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not necessary in all patients with acute SCI management. MRI is strongly recommended for the prognostication of acute SCI. The sagittal T2 sequence is particularly found to be of

by mansdocs.com

value. MRI should be used to direct clinical decision making. MRI has a role in clearance and ruling out of injury of the cervical spine in the obtunded patient only if there is abnormality of the neurological examination. MRI allows better visualization of the spinal cord, ligaments, disks, vessels, and other soft tissues than CT scans or radiographs. The main reason that limits MRI use in trauma is the logistics of patient transport and monitoring. The cephalo-caudal extent of cord edema can increase by an average of one full vertebral body level if imaging is performed 48–72 hours after injury, rather than within the first 24 hours. Within the first 5 days post injury, each 1.2-day delay to MRI increase the length of edema by one vertebral level. The exact time to perform an MRI is most often within the first 72 hours post injury. Four prognostication patterns are found to be predictive of neurological outcome (normal, single-level edema, multi-level edema, and mixed hemorrhage and edema). T2-weighted sequences can identify and measure the extent of both edema and hemorrhage within the spinal cord. On T2 MRI sequences, edema is seen as a hyperintensity of the signal within the cord and hemorrhage is seen as hypointensity. Hemorrhage is almost always present concurrently with edema, and on an MRI it is surrounded by a hyperintensity normally associated with edema. Regardless of their initial neurological status, all patients with a normal cord on MRI recover fully to ASIA grade E. The most severe neurological outcomes are associated with hemorrhagic pattern.

The clinician has to integrate clinical assessment including history and examination, plain X-ray, CT scan, both planar and two- or three-dimensional reconstructions and MRI scan. Whilst the MRI scan rarely adds significant additional information to the assessment of the anterior column it can be helpful in quantifying the degree of injury to the adjacent disk and other soft tissue. Two-dimensional CT reconstructions and the MRI scan are powerful modalities for identifying injuries in the posterior column. The clinical and radiological assessments, especially, the MRI scan should allow the clinician to identify the anatomical and functional level of the SCI, the degree of SCI, i.e. partial or complete and some quantification of the degree of soft tissue damage to the cord, including the presence of spinal shock. It has been shown that while single-level edema will resolve by 3 weeks, the signal from multi-level edema will persist beyond this time. The initial hypointensity of signal associated with hemorrhage has been shown to change into a hyperintensity of signal at 2 weeks.

CLEARANCE OF CERVICAL SPINE

In view of the severe consequences of a missed spinal injury, clearance of the cervical spine must only be undertaken by a suitably experienced specialist after adequate imaging. Neurological deterioration still occurs with missed spinal injuries. Cervical spine can be cleared in an awake patient with no spinal symptoms or in an awake patient with localized pain, normal plain imaging, CT scanning and normal flexion-extension X-rays of the painful part. The problems arise in obtunded or unconscious patients. Clearance of cervical spine in unconscious ICU patients remains controversial with no standard approach. Patients with a normal X-ray and fine slice CT scan can be said to have a 98% chance of no significant spinal injury, particularly unstable injuries or subluxation. Even the addition of MRI scanning does not give a 100% clearance and the recommended advice is that if plain X-ray and CT or MRI are normal then the intensive care staff should be instructed that there is only a very low chance of a potential instability in the spinal column, and that they should continue to use a lightweight orthosis and to log roll the patient until criteria for awake patients can be met. Any intervention before the neck is stable or fixed requires cervical in-line stabilization and log-rolling.

MANAGEMENT

Prehospital Management

Initial Stabilization

During the resuscitation and initial assessment phase, the cervical spine should be assumed to be injured. Patients should be immobilized before transport to a hospital and should be splinted using a cervical spine collar, two sandbags and a forehead tape for head immobilization. Padded boards or inflatable beanbag boards should be utilized to reduce pressure on the occiput and sacrum. Airway management of acute SCI patients requiring intubation in the prehospital setting should include the use of manual in-line cervical spine immobilization. Intubation of patients with acute SCI in the prehospital setting should not rely solely on cervical collar neck immobilization. Indirect methods of intubation may cause less cervical movement than with direct laryngoscopy with a Miller blade. Transport of patients with acute traumatic SCI to the definitive hospital center for care should occur within 24 hours of injury.

by mansdocs.com

Emergency Management

Evaluation

The main principles of evaluation are assessing and classifying the skeletal injury, assessing and classifying the neurological injury, assessing associated spinal injuries, identifying associated nonspinal injuries and establishing treatment priorities during the assessment phase.

Hospital/ICU Management

The most frequent predictor for ICU management is the need for both cardiovascular and pulmonary support. These depend on the level and severity of injury.

Respiratory

Respiratory complications are the leading cause of death in the long- and short-term. SCI can result in numerous pulmonary complications and special attention to respiratory support can reduce morbidity, length of stay, and mortality.

Respiratory Dysfunction

After SCI, intercostal muscle function is lost, with consequent failure of anterior-posterior expansion of the rib cage. More importantly, without intercostal contraction, as the diaphragm contracts, the chest wall is sucked in, causing paradoxical chest wall movement. Although innervation to the diaphragm is usually intact in lesions below C3, its function is also greatly affected post-SCI. Lost innervation to the lower thoracic segments causes the diaphragm to start at a more caudal position which increases its radius of curvature and, will reduce transdiaphragmatic pressure on contraction. Additionally, as the diaphragm descends, due to lost abdominal muscle tone, abdominal contents are pushed out and fail to provide the fulcrum needed to expand the lower chest. The lower rib cage is pulled in while the abdomen is pushed out resulting in the "see-saw" pattern of respiration seen. Finally, the diaphragm is pulled down by the weight of the abdomen, especially when upright, dramatically reducing apposition between diaphragm and chest wall. The rapid shallow breathing which ensues is inefficient. A greater percentage of each breath ventilates dead space and more time is spent in inspiration, when contracting muscles receive proportionally less of their blood flow. Lost abdominal muscle activity results in a decrease in maximal expiratory force and a reduced ability to cough, clear secretions, and protect the airway. Atelectasis increases the load placed on already compromised inspiratory muscles and *V/Q* mismatching occurs. Alveolar hypoventilation is inevitable and respiratory failure very common.

Some of these changes can be reduced by maintaining patients in a supine position. When supine, the weight of abdominal contents pushes the diaphragm higher into the chest, increasing apposition with the rib cage, reducing radius of curvature, and restoring the fulcrum lost with higher abdominal compliance. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in the supine position are higher when compared to the sitting position.

Respiratory Management

Respiratory management in SCI is required to prevent hypoxemia and respiratory complications and managing respiratory failure. SCI above the C4 level, copious sputum at 1 week, pneumonia, and major lobe collapse predict the need for ventilatory support. With C5 SCI around 50% will need short-term ventilation, SCI at C4 nearly all will need short-term ventilation and with C3 SCI around 50% will need permanent ventilation. 65% of patients of SCI needing ventilation are initiated within 48 hours. Respiratory insufficiency tends to be more prolonged when ventilation is required, usually occurring within the first few days but not infrequently lasting for weeks. The period at risk for intensive management of SCI patients appears to start very early if not immediately following the injury but may extend beyond a month due to prolonged ventilatory requirements that are frequently encountered. Respiratory insufficiency occurs in 70% of complete cervical injured patients and 27% of those with incomplete injury. SCI patients are at high risk for cardiovascular and pulmonary complications and often require intensive care related to those complications. Neurological outcome is improved and morbidity and mortality are reduced with management of SCI patients in specialized centers with standardized intensive care management with specific protocols established for the management of SCI within 24 hours. A significant improvement in vital capacity occurs within the first 5 weeks of injury with doubling by 3 months. Severity of cervical SCI was a predictor of ventilation and ICU length of stay. Cervical complete injured patients require a mean 30 days of ICU management. Work of breathing can be gauged by assessing

by mansdocs.com

patient comfort, trends in respiratory rate, and changes in the ability and quality of speech, and monitoring for increasing partial pressure of arterial carbon dioxide ($PaCO_2$). X-ray evidence of worsening volume loss, lobar collapse, and infection [together with white cell count (TLC), C-reactive protein (CRP), temperature, and sputum culture] require more aggressive treatment. Spirometry is an objective measure of respiratory reserve with FVC less than 12–15 mL/kg as an indicator for assisted ventilation.

Physiotherapy reduces accumulation of secretions and hence load placed on fatiguing muscles. Physiotherapists can assist coughing. Spontaneous cough can be augmented by moving the patient forward while seated, and applying intra-abdominal pressure to increase expiratory flow. It is contraindicated in patients with other injuries or spinal instability. Quad cough is a method applied for clearing secretions. External upper abdominal and lower costal margin pressure is exerted in time with a cough after a vital capacity breath.

Insufflation-exsufflation device—a portable electric device is very effective at clearing secretions by causing a rapid change in pressure gradient from positive to negative, increasing expiratory flow and instigating a cough. It can be applied by a face mask or via a tracheal tube or tracheostomy and patient satisfaction is high.

Abdominal binding and nursing patients supine can offset the decline in pulmonary function due to flaccid abdominal muscles.

Bronchoscopy is the most direct way of clearing secretions, obtaining bronchoalveolar lavage specimens, and re-inflating collapsed lung segments.

Frequent turning of patients is necessary to avoid pressure sore formation and to prevent atelectasis. Supine, rotating, and percussive beds are available to mechanize this. Early surgical stabilization allows for mobilization and removal of halo jackets (which reduce lung volumes), although early surgery increases the need for postoperative ventilation.

Exercise training (upper and lower body exercises) results in increased maximal oxygen uptake, increased muscle strength, and improved muscle coordination.

Respiratory Complications

Respiratory complications are common and the major cause of ICU admissions. They include atelectasis, retention of respiratory secretions, pneumonia and acute respiratory failure. The level and completeness of the injury are associated with a higher likelihood of respiratory complications. Respiratory rate at admission (tachypnea), increased age, and previous respiratory disease correlates with the occurrence of pulmonary complications. Specific factors associated with an increased risk of significant respiratory failure include high cervical (above C5 level) injury, increased injury severity (especially ASIA grade A injury), advanced age, prior respiratory disease, trauma, and tachypnea at admission. As much as 50% of patients with a complete lesion of the cervical or thoracic spinal cord develop atelectasis or pneumonia within 30 days of the injury, with the peak incidence at 3–5 days. Atelectasis and copious secretions stand out as frequent obstacles to ventilator weaning and discharge from the ICU. Delayed pulmonary complications must also be anticipated.

Most early deaths are due to pulmonary complications. Respiratory complication rates were highest with C1–4 SCI (84%) but are also frequent in lower cervical and thoracic SCI (60% and 65%, respectively). The incidence of respiratory complications and ventilatory failure occurs at around 4–5 days and need ventilator support around 30 days (20% requiring greater than 8 weeks of ventilation). Pneumonia and atelectasis tend to present in a more delayed fashion. A cohort of patients experience delayed apnea between days 9 and 15 following a period of clinical stability, thus emphasizing that pulmonary complications may be more delayed. Those able to start ventilatory weaning earlier also are able to wean faster.

Endotracheal Intubation with Cervical Spinal Injury

Intubation when required has to be done without movement of the cervical spine. The options are awake fiberoptic nasotracheal intubation or orotracheal intubation under anesthesia. Awake fiberoptic nasotracheal intubation depends on the skill of the medical staff and availability of equipment but cannot be done in an emergency situation. In orotracheal intubation, the anterior part of the cervical collar is removed, manual online stabilization of the head is performed, sedation/muscle paralytic agents are given and intubation is done with cricoid pressure with the help of a bougie taking care not to extend the cervical spine.

Tracheostomy

A tracheotomy for pulmonary support, weaning or to protect the airway is necessary in 69–77% of patients with complete tetraplegia during their hospital stay. There

by mansdocs.com

is relative unanimity in that the incidence of pulmonary infections reduces significantly following tracheotomy and that the rate of pulmonary infections increases with the duration of endotracheal intubation. Both cervical level and severity are predictive of the need for tracheotomy. Tracheostomies have clear advantages, especially when weaning may take weeks. Patients find them comfortable, and they minimize laryngeal damage from prolonged intubation, have less dead space compared with a tracheal tube, and are associated with fewer respiratory infections. Tracheostomy interferes with surgical anterior fixation.

Weaning from Mechanical Ventilation

C1–3 tetraplegics who cannot be weaned are managed with domiciliary ventilation. Patients with an SCI of C4 and below are potentially weanable, but only once active pulmonary pathology has resolved and the chronic changes to pulmonary mechanics have commenced. After SCI, intercostal muscles are initially flaccid, but over the ensuing weeks, spasticity develops and the chest wall becomes more rigid with fewer tendencies to collapse with inspiration. Individuals with cervical SCI continue to experience compromised expiratory muscle function, but the action of the clavicular portion of pectoralis major muscle, by compressing the rib cage and increasing intrathoracic pressure, can contribute to an improved cough.

After conversion to pressure support (PS) ventilation and in the absence of mandatory ventilation, two common weaning strategies exist. PS weaning, where incremental reductions in the level of PS are carried out until ultimately patients are converted to high flow or continuous positive airway pressure (CPAP) breathing and T-piece weaning (progressive ventilator-free breathing) or "sprint weaning". Once PS levels reach 12–15 cm H_2O, rather than reducing PS further, patients breathe without PS either on a high flow circuit (with or without CPAP) or simply through a heat and moisture exchange (HME) device, for a predetermined time every hour. The duration free of PS is gradually increased (sometimes by as little as a few minutes per hour) until they can attain full or partial independence from mechanical assistance. It is important that during "sprinting" patients are rested at night to prevent exhaustion. Studies suggest that T-piece weaning is as effective or better when compared with PS weaning with both superior to synchronized intermittent mandatory ventilation (SIMV) weaning.

Non-Invasive Ventilation

Continuous positive airway pressure can increase functional residual capacity (FRC) thereby improving compliance and reducing work of breathing, but excessive CPAP can increase work of exhalation. Bilevel or pressure-assisted noninvasive ventilation (NIV) is usually more beneficial, increasing minute ventilation and providing assistance to overloaded and failing muscles. NIV may be useful before surgery and as a means of offsetting intubation or as a step down after tracheal extubation or decannulation.

Cardiovascular

Cardiovascular Dysfunction

In cervical SCI, there is loss of supraspinal control of the heart and peripheral vasculature with unopposed vagal action. Hypotension occurs with lesions above T6 due to loss of sympathetic autonomic function and unopposed parasympathetic function. In the early phase of spinal (neurogenic) shock, there is loss of autonomic reflex activity in the isolated cord segment. These lead to bradycardia and hypotension associated with loss of vasoconstrictor tone leading to vaso-/venodilatation and venous pooling. They are more prone to hypotension with posture change, hypovolemia and ventilation. Loss of cardiac accelerator fibers results in bradycardia and patients are unable to increase cardiac output by changes in heart rate. Although the duration of neurogenic shock is variable, recovery tends to be incomplete and postural hypotension can be a persistent problem.

Cardiovascular Management

Electrocardiogram (ECG), blood pressure, central venous pressure and urine output should be monitored. Fluids should be administered. Vasopressors should be used to keep the mean arterial pressure at 85–90 mm Hg for the first 7 days to avoid ischemic injury to the cord. Since cardiac output is the product of heart rate and stroke volume, preserving stroke volume is essential. Neurogenic shock is initially managed by fluid resuscitation and hypovolemia is poorly tolerated. Induction of anesthesia and institution of intermittent positive pressure ventilation (IPPV) will exacerbate hypotension. If fluid resuscitation alone is inadequate, vasoactive drugs should be used to achieve a mean arterial pressure of 80 mm Hg within the first 72 hours post injury to optimize cord perfusion (and prevent

by mansdocs.com

secondary ischemia). Alpha-agonists (phenylephrine and noradrenaline) are preferred, but bradycardias may occur in conjunction with α-agonists. Adrenaline can be used; however, glycopyrrolate or atropine usually suffices to increase heart rate. The period of cardiovascular instability, which is often due to sympathetic dysfunction, is most pronounced acutely and the period at risk of 1 week and 2 weeks exists. With regard to hypotension, patients are most vulnerable during the first week.

Cardiovascular Complications

The predictors of cardiovascular complications are high cervical and complete SCI. 90% of patients with complete cervical (ASIA grade A) SCI require vasopressor support. This incidence is less in incomplete SCI (50%) and with thoracic SCI (30%). 16% of patients have systolic blood pressure less than 90 mm Hg at admission and 82% exhibit volume-resistant hypotension within the first 7 days. All severe cervical SCI patients experience bradycardia. Hypotension, use of pressors, and cardiac arrest are only observed in severe cervical SCI (68%, 35%, and 16%, respectively). A significant number of SCI patients require cardiovascular support with fluids and vasopressor therapy and that the incidence of these events is correlated with the severity of injury and is higher with cervical SCI and when hypotension is present at admission. Patients are at risk of cardiovascular events related to disturbance in sympathetic function in the first 14 days. If these complications occur, they resolve within 2–6 weeks. Endotracheal suctioning often required for pulmonary toilette in SCI patients (especially cervical SCI) is associated with severe bradycardia and cardiac arrest in 10% of patients within the first 2 weeks of injury. This can be prevented by premedication with atropine. Some patients will need temporary pacemaker insertion for symptomatic bradycardia and cardiac arrest.

Venous Thromboembolism

The incidence of venous thromboembolism is around 40% without prophylaxis with pulmonary embolism accounting for 15% of deaths in the first year. Prophylaxis is provided by combining graduated compression stockings (GCS) with low-molecular-weight heparin (LMWH) within 72 hours. Heparin prophylaxis is inadequate when used alone. Where heparin is contraindicated, GCS should be combined with intermittent pneumatic compression. In addition, femoral access contributes to venous stasis and should be avoided. Prophylaxis should continue for 3 months and, during convalescence, oral anticoagulants (INR 2–3) can be substituted for LMWH.

Neurological

There is continued controversy around the role of high dosage methylprednisolone in reducing the impact of SCI. Each hospital, region or country have their own protocol and accepted standard of care, but if the local preference is to use the steroid protocol then this should be instituted as soon as the SCI has been diagnosed and this may well be very early on in the assessment process.

The aim of the treating surgeon should be to reverse and certainly prevent deterioration of the neurological injury, to either identify adequate spinal stability to allow early mobilization or to achieve such stability by the use of modern surgical techniques such that patients can be rapidly rehabilitated to their previous state, social and sporting activities.

Skeletal

Skeletal management includes adequate reduction, maintenance of position and immobilization until stability has been achieved. Conservative measures include closed reduction, traction with head tongs or collars. Early surgical intervention (from 8 hours to 24 hours) should be considered following acute traumatic SCI for achieving early stability and pain control, early mobilization and rehabilitation.

OUTCOME

Outcomes can be improved by management in specialized centers with access to intensive care. The prehospital immobilization of patients using a cervical collar, head immobilization, and a spinal board, utilization of padded boards or inflatable beanbag boards to reduce pressure, transfer of patients off of spine boards as soon as feasible, including transfer of patients off spinal boards while awaiting transfer from one hospital institution to another hospital center for definitive care, inclusion of manual in-line cervical spine traction for airway management in patients requiring intubation in the prehospital setting, transport of patients with acute traumatic SCI to the definitive hospital center for care within 24 hours of injury, and training of emergency medical personnel in the prehospital setting to apply criteria to clear patients of cervical spinal injuries, and immobilize patients suspected of having cervical spinal injury improves outcome.

by mansdocs.com

Neurological Recovery

Patients with single-level edema have better initial neurological status than patients with diffuse edema. Single-level edema patients show an improvement of about two grades in ASIA score compared to an improvement of one grade for patients with diffuse edema. The prognosis of patients with edema is significantly better than for those with hemorrhage. Hemorrhage, the number of levels of edema, greater degree of cord compression, greater degree of canal compromise, and severity of soft tissue injury are associated with a worse neurological outcome. Single-level hemorrhage alone often indicates a complete lesion (ASIA grade A).

Survival

Dying due to traumatic SCI may involve a high cervical level lesion causing respiratory insufficiency, consequences of traumatic SCI (e.g. autonomic dysfunction) and complications (e.g. infections). In-hospital mortality rates after acute traumatic SCI varies from 3.6% to 11.9%. The 1-year mortality rate will be slightly more. Factors that apparently affect mortality include inefficient transfer logistics, initially missed spinal instability, and unsuccessfully treated complications. Respiratory complications are the leading cause of death in the long- and short-term. SCI can result in numerous pulmonary complications and special attention to respiratory support can reduce morbidity, length of stay, and mortality.

BIBLIOGRAPHY

1. Casha S, Christie S. A systematic review of intensive cardiopulmonary management after spinal cord injury. J Neurotrauma. 2011; 28:1479–95.
2. Chhabra HS, Arora M. Demographic profile of traumatic spinal cord injuries admitted at Indian Spinal Injuries Centre with special emphasis on mode of injury: a retrospective study. Spinal Cord. 2012;50:745-54.
3. Denton M, McKinlay J. Cervical cord injury and critical care. Cont Edu Anaesth Crit Care and Pain. 2009;9:82-6.
4. Fehlings MG, Cadotte DW, Fehlings LN. A Series of systematic reviews on the treatment of acute spinal cord injury: A foundation for best medical practice. J Neurotrauma. 2011; 28:1329–33.
5. Goldberg AL, Kershah SM. Advances in imaging of vertebral and spinal cord injury. J Spinal Cord Med. 2010;33(2): 105–16.
6. Gutteridge GA, Spinal injuries, Bersten AD, Soni N, Oh's Intensive Care Manual, 6th edition. Butterworth-Heinemann; 2009. pp. 803-13.
7. O'Dowd JK. Basic principles of management for cervical spine trauma. Eur Spine J. 2010;19:S18–S22.
8. Shao J, Zhu W, Chen X, et al. Factors associated with early mortality after cervical spinal cord injury. J Spinal Cord Med. 2011;34(6):555-62.

by mansdocs.com

CHAPTER

39

Neurocritical Care Management of Subarachnoid Hemorrhage

Mukesh M Gupta, Vimal K Agarwal, Girish Rajpal

INTRODUCTION

Subarachnoid hemorrhage (SAH) is intracranial hemorrhage that lies in the space between the thin arachnoid layer and pia mater. Causes of SAH broadly divided into traumatic and nontraumatic (spontaneous). Most common cause of SAH is traumatic due to traumatic brain injury (TBI). From 12% to 53% of TBI patients have SAH on initial computerized tomography (CT) scanning. Presence of SAH in TBI has a significant impact on patient outcome. In contrast to traumatic SAH, spontaneous or nontraumatic SAH occurs less frequently, and its etiology is more diverse. Most common cause of spontaneous SAH is rupture of an intracranial aneurysm (85%) in the basal cerebral arteries, leading to escape of blood at high pressure into the subarachnoid space. Others causes of spontaneous SAH are cerebral arteriovenous malformations (4–5%), perimesencephalic or pretruncal nonaneurysmal SAH, vasculitis, carotid or vertebral artery dissection, cerebral venous thrombosis, pituitary apoplexy, brain tumor bleed, spinal arteriovenous malformations and coagulation disorders (Table 1).

Aneurysmal SAH represents only 3–5% of overall stroke but accounts for a large loss of productive life years because it commonly occurs in younger people, peaking between 40 and 60 years. Aneurysmal SAH is a devastating disease

Table 1: Causes of subarachnoid hemorrhage.

Category	*Causes*
Idiopathic	Benign perimesencephalic subarachnoid hemorrhage
Infections	Bacterial, tuberculous, and fungal meningitis; syphilis; herpes simplex or other viral encephalitis; leptospirosis; listeriosis; brucellosis; yellow fever; typhoid fever; dengue; malaria; anthrax
Trauma	Head injury, electrical injury
Toxins	Amphetamines, cocaine, monoamine oxidase inhibitors, epinephrine, alcohol, ether, carbon monoxide, morphine, nicotine, lead, quinine, phosphorus, pentylenetetrazol, hydrocyanic acid, insulin, snake venom
Vascular	Atherosclerosis; rupture of hypertensive, amyloid, or other type of intracerebral hemorrhage into cerebrospinal fluid; hemorrhagic transformation of ischemic infarction; ruptured arteriovenous or other vascular malformation; vasculitis from systemic lupus erythematosus or polyarteritis nodosa; eclampsia; intracranial venous thrombosis secondary to pregnancy, oral contraceptives, volume depletion, hypercoagulable states, trauma, or infection
Blood diseases	Leukemia, hemophilia, sickle cell anemia, pernicious anemia, aplastic anemia, agranulocytosis, thrombocytopenic purpura, polycythemia vera, Waldenström's macroglobulinemia, lymphoma, myeloma, hereditary spherocytosis, afibrinogenemia, liver diseases associated with coagulopathy, disseminated intravascular coagulation, acquired coagulopathies secondary to anticoagulant drugs
Neoplasm	Glioma, meningioma, hemangioblastoma, choroid plexus papilloma, chordoma, hemangioma, pituitary adenoma, sarcoma, osteochondroma, ependymoma, neurofibroma, bronchogenic carcinoma, choriocarcinoma, melanoma.

by mansdocs.com

Table 2: Modified Hunt and Hess subarachnoid hemorrhage grading scale.

Grade	Sign and symptoms	Percent risk of death as originally reported by Hunt and Hess
0	Unruptured aneurysm	
1a	No acute meningeal signs, fixed neurodeficit	
1	Mild headache, slight nuchal rigidity	11
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	26
3	Drowsiness, confusion, mild focal neurological deficit	37
4	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbance	71
5	Deep coma, decerebrate rigidity, moribund appearance	100

Table 3: World federation of neurological surgeons (WFNS) SAH grading scale.

Grade	GCS score	Presence of aphasia, hemiparesis or hemiplegia	Percentage of patient with poor outcome at 1 month after discharge (GOS1-3)
0	Unruptured aneurysm	–	
1	15	–	20
2	13–14	–	53
3	13–14	+	70
4	7–12	±	85
5	3–6	±	93

(SAH: Subarachnoid hemorrhage; GCS: Glasgow Coma Scale).

with an incidence of 2–22.5 per 100,000 persons each year. One-month case fatality is as high as 35% even in high income countries, and around one-third of those who survive need life-long care, with a further third having residual cognitive impairment that affects their functional status and quality of life. Mortality is higher and good functional outcome less likely in patients with poor grade SAH, those over 65 years of age and those who develop complications.

Early aggressive resuscitation and multidisciplinary intensive care management are associated with improved outcomes and consensus guidelines for the intensive care management of SAH have recently been published.[1]

CLINICAL PRESENTATION

The classic history of aneurysmal SAH is one of sudden onset of severe headache, often described as the "worst imaginable" accompanied by nausea, vomiting and transient loss of consciousness. However, this is nondiscriminatory and only around 1% of patients presenting to emergency departments with headache will subsequently be diagnosed with SAH. Photophobia, neck stiffness and backache can occur as a result of meningeal irritation. Patient may have other clinical features range from altered consciousness, seizures, cranial nerve palsy and hemiparesis or hemiplegia to coma. In traumatic SAH, history of trauma is present and its clinical presentation depends on the severity of TBI.[2]

Several SAH grading scales have been described but the modified Hunt and Hess (Table 2), based on neurological status and World Federation of Neurological Surgeons (WFNS) scale (Table 3), based on the Glasgow Coma Scale (GCS) and presence of motor deficits, is most commonly used because of its simplicity and objectivity. These scales not only guide patient management that is influenced by the severity of the SAH, but also offer an early estimation of patient prognosis.[2,3]

DIAGNOSIS

Standard noncontrast computed tomography (NCCT) head is the investigation of choice for SAH and is diagnostic in up to 97.5% of cases (Fig. 1). A normal scan does not exclude SAH and, in the presence of a good history and normal scan, guarded lumbar puncture (<10 mL) can be performed. Confirmation of the presence of red blood cells or their metabolites in the cerebrospinal fluid (CSF) identifies an additional 3% of patients who subsequently have an aneurysm detected by cerebral angiography. The diagnostic sensitivity of lumbar puncture is increased when performed at least 6–12 hours after the initial ictus, although this results in a delay in initiating treatment. Immediate CT angiography (CTA) is an appropriate first step to identify the anatomical territory of the aneurysm and interpretation reliably identifies aneurysms size greater than 4 mm. Four-vessel digital subtraction angiography (DSA) with 3-D reconstruction remains the investigation of choice should be plan on urgent basis to identify the source of SAH and anatomy and characterization of ruptured intracranial aneurysm. Additional imaging can

by mansdocs.com

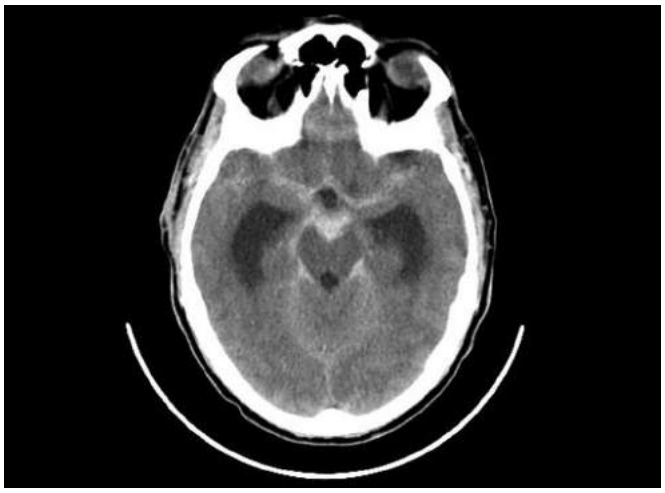


Fig. 1: Diffuse subarachnoid hemorrhage.

inform treatment planning, particularly required in poor grade patients. A repeat CT scan may be necessary to confirm the diagnosis, identify acute hydrocephalus and allow treatment planning of the causative aneurysm. Perfusion CT quantifies regional and global hypoperfusion, and various magnetic resonance imaging (MRI) sequences identify ischemia and provide a wealth of information on metabolic and perfusion variables.[4]

NEUROMONITORING IN SAH

Multimodal cerebral monitoring, including intracranial pressure (ICP), brain tissue oxygen tension, transcranial Doppler ultrasonography (TCD), cerebral microdialysis and electrophysiological monitoring, allows integration of multiple aspects of cerebral physiology with systemic physiological variables. In this way individualized patient care can be delivered with the aim of preventing or minimizing secondary ischemic injury. After SAH, this is particularly relevant in terms of balancing cerebral oxygen supply and demand in the setting of acute injury and in the subsequent detection and treatment of delayed cerebral ischemia (DCI). ICP is increasingly being monitored, particularly in poor grade patients, as the need for aggressive management of intracranial hypertension is undisputed. This can be achieved via a ventricular catheter placed to relieve hydrocephalus or via a standard transducer tipped intraparenchymal monitor. Changes in brain tissue biochemistry and oxygenation may identify impending or actual cerebral hypoxia or ischemia before changes in other monitoring modalities or the patient's clinical status is apparent. Although this extends the potential treatment window, it remains to be determined whether interventions directed toward normalization of these biomarkers will result in improved clinical outcome. Impaired vascular reactivity has been linked with poor outcome after SAH, and integration of cerebral monitoring signals can be used to derive indices of cerebrovascular reactivity.

There is recent interest in electrophysiological monitoring after SAH. Nonconvulsive seizures and status epilepticus occur more frequently than previously recognized and continuous electroencephalography has a key role in their detection and therefore management. Cortical spreading depolarizations (SDs) are pathological events characterized by near-complete sustained depolarization of neurons and astrocytes that result in secondary injury related to mitochondrial damage, accumulation of intracellular calcium and excitotoxicity. SDs may occur in up to 70% of patients after SAH but their detection currently requires placement of an electrode strip directly onto the brain surface, thus limiting routine monitoring on the ICU. There is currently no consensus regarding multimodal monitoring in patients with SAH and the majority of modalities have not been thoroughly validated nor their influence on outcome determined.[5]

MANAGEMENT OF SAH AND ITS COMPLICATIONS

Acute treatment is similar to that for any critically ill patient and focuses on maintenance of adequate ventilation and hemodynamic stabilization. In addition, attention must be given to maintenance of cerebral perfusion, minimizing the risk of rebleeding and achieving a rapid diagnosis. This presents many challenges in the emergency department as multiple goals must be achieved simultaneously, often remote from neuroscience input. Unconscious patients, or those with a falling GCS, should be intubated and ventilated to maintain PaO_2 greater than 100 mm Hg and $PaCO_2$ 30–35 mm Hg. Short-term moderate hyperventilation ($PaCO_2$ 30–35 mm Hg) may be indicated if intracranial hypertension is suspected, e.g. in the presence of hydrocephalus, an expanding intraparenchymal hematoma or cerebral edema. Hypertension is a normal response to SAH, although high blood pressure increases the risk of rebleeding, whereas excessive reductions in blood pressure risk the development of cerebral ischemia. Extreme hypertension should be treated cautiously with short-acting agents, but modest elevations in blood pressure [mean ambulatory blood

by mansdocs.com

pressure (ABP) <110 mm Hg] do not require treatment. Prior to securing the aneurysm, premorbid blood pressure should be used to refine pressure targets, although mean ABP is usually maintained between 90 mm Hg and 110 mm Hg. Hypotension should be meticulously avoided. Once the poor grade patient is stabilized, immediate transfer to a neurosciences center should be undertaken. Stable patients with good grade SAH should be transferred urgently so that definitive treatment can be undertaken within 24 hours of the ictus. Recent guidelines recommend that patients with SAH should be treated at high-volume centers with timely access to multidisciplinary teams since this is associated with improved outcomes.

Definitive treatment for aneurysmal SAH is obliteration of aneurysm. Early aneurysm control reduces the risk of rebleeding and allows preventing or treating cerebral hypoperfusion due to cerebral vasospasm. Options for treatment are only two, i.e. (i) neurosurgical clipping and (ii) endovascular coiling. The widespread use of endovascular coiling of intracranial aneurysms represents a major advance in the treatment of SAH because minimally invasive and effective treatment is possible even in the sickest patients. The International Subarachnoid Aneurysm Trial (ISAT) compared endovascular and surgical techniques and confirmed an improvement in early survival in selected patients receiving endovascular therapy with a small excess of late bleeds.[6] ISAT has been criticized for many reasons. In brief, 69% of the 9,559 patients eligible for recruitment into the study were excluded because of lack of equipoise. Since almost all intracranial aneurysms can be treated by surgery, it follows that a large proportion of patients was excluded because of an assessment that their aneurysm was not suitable for endovascular coiling. There was a rarity of posterior circulation and middle cerebral artery aneurysms in ISAT and, because posterior circulation and middle cerebral artery aneurysms are preferentially treated by coiling and clipping respectively, this also raises the possibility of sample bias. However, the proportion of cases that are unsuitable for endovascular treatment is likely to be much lower today because of advances in technology and expertise after this study.

The majority of aneurysms is now primarily treated by endovascular options, but coiling is still not a replacement for neurosurgical treatment. Intracranial aneurysms in selected locations (those greater than 25 mm, those with a wide neck or with branches arising from the aneurysm) may not be amenable to endovascular coiling and some may have a worse outcome with coiling compared to clipping. Since then most of these uncoilable aneurysms are now being treated by balloon or stent assisted coiling and lately flow diverter stents also. Each patient and aneurysm is different and a treatment decision must be made for each patient individually by a multidisciplinary team.

Following securing of the aneurysm, the intensive care management of SAH involves treatment of acute complications such as hydrocephalus requiring external ventricular drainage, optimization of systemic physiology and the prevention or treatment of delayed cerebral ischemia (DCI) and non-neurological complications. Aggressive treatment is now recommended for all but the most hopeless cases since substantial numbers of even poor grade patients may do well following comprehensive multidisciplinary therapy.

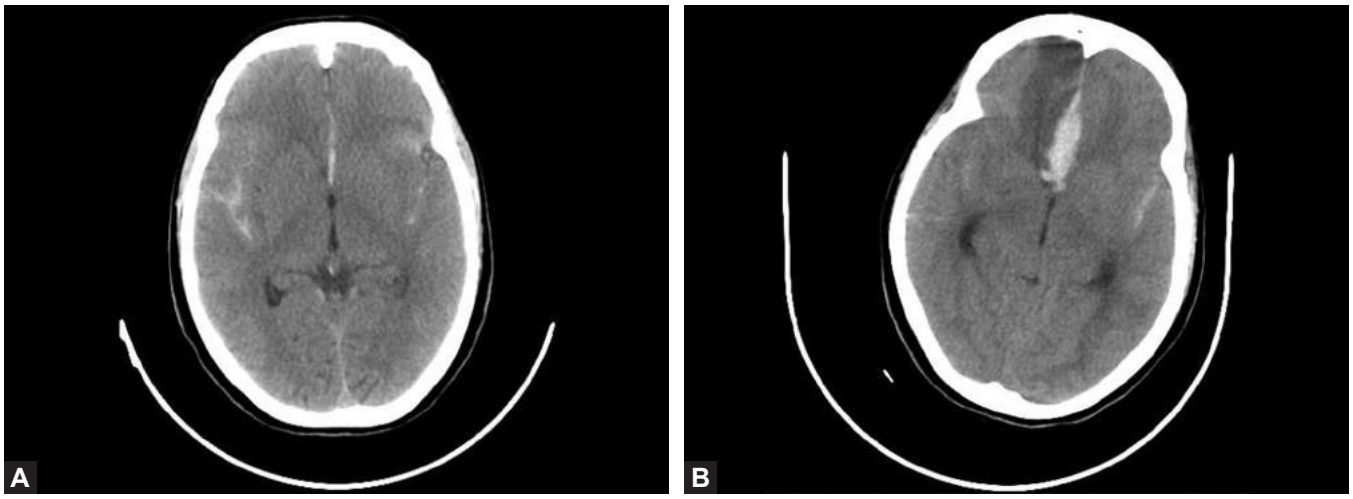
Nevertheless, some patients will have a poor outcome despite maximal therapy and it is essential that early aggressive treatment is linked to compassionate end-of-life care if a satisfactory degree of clinical recovery does not occur within an appropriate time scale.

Neurological Complications of SAH

Rebleeding

After initial hemorrhage and vasospasm, rebleeding is the highest cause of mortality in patient with aneurysmal SAH. Rebleeding was previously the primary cause of death following poor grade SAH, but rates have dramatically reduced since the shift toward early securing of the ruptured aneurysm. The greatest risk of rebleeding occurs within the first 24 hours and is highest in those with the poorest SAH grade. Earlier study showed that rebleeding rates are 4% in first 24 hours, 1–2% per day for next 2 weeks and 50% for first 6 months and 3% per year following ictus. Definitive treatment to prevent rebleeding is early obliteration of aneurysm. Another intervention that has been studied is the use of acute antifibrinolytic therapy. This may reduce the risk of rebleeding by as much as 40% but is not associated with improved outcome, possibly because of microthrombosis related cerebral ischemia. The short-term use of antifibrinolytics should currently be considered only in those at high risk of rebleeding and in whom definitive treatment of the aneurysm is delayed (Figs. 2A and B).

by mansdocs.com



Figs. 2A and B: Rebleeding due to anterior communicating artery (ACOM) aneurysm (anterior interhemispheric subarachnoid hemorrhage).

Delayed Cerebral Ischemia

Delayed cerebral ischemia is a term applied to any neurological deterioration, including focal neurological deficits and altered consciousness, which persists for more than 1 hour and cannot be explained by other abnormalities identified by radiographic, laboratory or electrophysiological investigations. It may be unrecognized clinically in some patients because of their poor clinical grade or the concurrent administration of sedatives. DCI occurs in around 30% of patients, peaks between 4 and 10 days after the ictus and persists for several days. It is second only to the initial hemorrhage as a cause of morbidity and mortality after SAH.

Pathophysiology: Although DCI has been attributed to cerebral vasospasm, the exact relationship between the two is unclear. DCI can occur in the absence of vasospasm and vice versa, and ischemia often involves more than one vascular territory. Other mechanisms contributing to DCI include vascular dysautoregulation, microthrombi, direct neurotoxic effects and cortical SDs.

Diagnosis: Delayed cerebral ischemia is detected clinically by a reduction in level of consciousness with or without a focal neurologic deficit. In unconscious or sedated patients, several methods can be used to identify DCI but 4-vessel cerebral DSA remains the diagnostic gold standard. The risks and time requirements of this invasive intervention mean that alternative and complementary diagnostic tools, such as CTA and CT perfusion, which together allow characterization of vascular anatomy and associated cerebral perfusion abnormalities are increasingly being used. Transcranial Doppler measures blood flow velocity (FV) in basal cerebral arteries, and consecutive TCD examinations should be carried out after SAH; blood FV greater than 120–140 cm/s, or FV increases more than 50 cm/s/day from baseline is generally accepted to be indicative of developing or established DCI. However, there is considerable interindividual variation and a recent study analyzing 1,877 TCD examinations found that almost 40% of patients with clinical evidence of DCI never had FVs that exceeded 120 cm/s. Treatment decisions should not therefore be based on TCD findings alone. As changes in the cerebral blood flow (CBF) affect FV, the Lindegaard ratio, which compares FV in the ipsilateral middle and internal carotid arteries and is unaffected by changes in CBF, is often used. A ratio greater than 3.0 is indicative of vasospasm and values greater than 6 suggest severe spasm. Multimodal monitoring, particularly brain tissue PO_2 and cerebral microdialysis, might also identify vasospasm and identify treatment targets, although these are focal techniques and the monitoring probe must be accurately located in the region of interest.

Treatment: Since DCI is delayed and may be reversible, it is an obvious target for preventative and treatment strategies. All patients should receive enteral nimodipine, a specific antagonist of L-type voltage-gated calcium channels, 60 mg 4 hourly immediately after diagnosis. This reduces the incidence of DCI and improves outcome. The mechanisms by which nimodipine reduces DCI are uncertain because it does not reverse angiographic vasospasm in humans. Although intravenous nimodipine

by mansdocs.com

is sometimes used in critically ill patients, this route of administration is unproven and care must be taken to avoid hypotension.[7]

Triple-H therapy (hypervolemia, hemodilution and hypertension) has been widely used to prevent and treat DCI but the combination has never been tested in a randomized controlled trial. While fluid therapy is a key component of the management of SAH, prophylactic hypervolemic therapy is not effective in raising CBF or improving neurological outcome, and there is some evidence of harm from overly aggressive filling. Recent consensus guidelines recommend that euvolemia rather than hypervolemia should be the target for both prophylaxis and treatment of DCI, and that hemodilution should not be used. Isotonic crystalloids are the fluids of choice, although hypertonic saline solutions have a place in patients who are hyponatremic. In the presence of a secured aneurysm, maintenance of ABP at supranormal levels is the mainstay of treatment of DCI. Pressure should be increased in a stepwise fashion, guided by assessment of neurological function, neuromonitoring or radiological evidence of improved perfusion. In the presence of adequate volume status, noradrenaline is widely used to augment ABP. Central venous pressure is an unreliable indicator of volume status after SAH and although invasive ABP and cardiac output monitoring are often used to guide goal-directed volume and vasopressor therapy, no technology has been demonstrated to be superior to another.[8]

Endovascular treatment options for cerebral vasospasm are effective in some cases which are resistant to medical therapy. Balloon angioplasty has been widely used to reverse vasospasm in major basal arteries. Angioplasty is often combined with the selective intra-arterial administration of vasodilators, including verapamil, nimodipine, nicardipine, milrinone and fasudil, although comparisons with conventional (non-interventional) therapy have been made.[9]

Since DCI is unlikely to be related only to vasospasm, several pharmacological agents have been tested in this context. Statins have multiple beneficial effects on vascular function and have been used to prevent and treat DCI. However, a recent meta-analysis found that statins have no significant effect on the incidence of DCI, poor neurological outcome or mortality. Current guidance recommends that patients already on statins should have these drugs continued but that the introduction of acute statin therapy should only be considered in carefully selected patients at high risk of DCI. The ongoing Simvastatin in aneurysmal subarachnoid hemorrhage (STASH) trial is designed to determine the outcome effects of statins after SAH (http://clinicaltrials.gov/ct2/show/NCT00731627). Magnesium reverses cerebral arterial spasm in animal models of SAH, but the only randomized clinical trial demonstrated no beneficial effect on the incidence of DCI and cerebral infarction or on clinical outcome. A subsequent post hoc analysis showed that high plasma magnesium levels are associated with worse clinical outcomes, although hypomagnesemia should be avoided, induced hypermagnesemia is therefore not recommended.[10] Endothelin has a key role in maintaining vascular tone and endothelin-A antagonists, such as clazosentan, have been studied but have not been shown to reduce mortality or improve neurological outcome after SAH.[11] Since activation of the coagulation cascade and microthrombosis might play a role in DCI, attention has also focused on agents affecting these variables. A Cochrane review suggested a nonsignificant trend toward improved outcome in patients treated with antiplatelet agents, but this was accompanied by an increased risk of hemorrhagic complications. Two large randomized controlled trials provided contradictory results about the effect of enoxaparin on outcome after SAH and, although antifibrinolytic agents reduce the rates of rebleeding-related mortality, this is offset by a higher rate of DCI.[12,13]

Hydrocephalus

Hydrocephalus is a known complication of SAH; its incidence varies widely, range from 15% to 53%. Hydrocephalus following aneurysmal SAH can be of both the obstructive and the communicating variant. In obstructive hydrocephalus, there may be intraventricular extension of the subarachnoid blood or an intraparenchymal hematoma. In the communicating variant the ventricular system may be free of blood, but the arachnoid granulations may become obstructed by the subarachnoid blood, limiting reabsorption of CSF. Recognition of the cause of the patient's hydrocephalus is important as it can affect the means by which the hydrocephalus is treated (lumbar drain, external ventriculostomy drainage, endoscopic third ventriculostomy, shunt and so forth). Things that are important to the neurointensivist include ventriculostomy or lumbar drain weaning, risk of aneurysmal rebleeding in the setting of cerebrospinal fluid drainage and indications and timing of permanent cerebrospinal diversion (i.e shunting) (Fig. 3).

by mansdocs.com

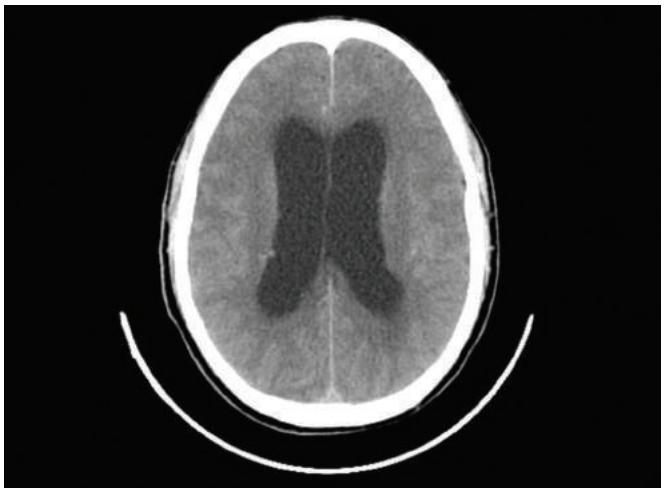


Fig. 3: Post subarachnoid hemorrhage hydrocephalus.

Seizure Control

Seizures occur in approximately 10–15% of patients after SAH but treatment remains controversial. Actual seizures must be treated aggressively, but universal prophylaxis is not recommended. Three days of treatment offers similar seizure prevention and better outcome than long-term therapy. Phenytoin should be avoided because of associated cognitive effects and poor outcome, and, a short course of l500–1000 mg levetiracetam every 12 hourly, is recommended for seizure prophylaxis. The duration of therapy is tailored to the individual patient, and takes into account the extent and location of SAH or intraparenchymal hemorrhage and the presence or absence of seizures.[14]

Non-Neurological Complications of SAH

Non-neurological complications are common after SAH and independently associated with poor outcome. In a study from a single center, 79% of patients developed at least one medical complication and, in the Cooperative Aneurysm Study, the proportion of deaths related to non-neurological complications was 23% (similar to that of vasospasm at 22%). As they are independently associated with poor outcome after SAH, non-neurological complications represent potentially modifiable risk factors and early recognition and prompt intervention might therefore improve outcome. However, the intensive care management of non-neurological organ dysfunction and failure presents significant challenges because optimum treatment for the failing systemic organ system may have potentially adverse effects on the injured brain.[15]

Cardiopulmonary Complications

Cardiac complications are common and associated with DCI and poor outcome. These are manifest as an abnormal ECG, elevated cardiac troponin (cTnI), and a spectrum of ventricular dysfunction collectively referred to as the neurogenic stunned myocardium (NSM) syndrome. ECG abnormalities are extremely common after SAH, elevation of cardiac cTnI occurs in 20–40% of patients and left ventricular (LV) dysfunction in around 18%. NSM is caused by excessive noradrenaline release from myocardial sympathetic nerve terminals resulting in a physiological myocardial denervation in the presence of normal coronary perfusion. This results in a characteristic pattern of LV regional wall motion abnormalities involving the basal and middle portions of the anteroseptal and anterior ventricular walls with relative apical sparing, reflecting the distribution of sympathetic nerves rather than specific vascular territories. The degree of myocardial dysfunction and damage is related to the severity of the SAH and, although LV dysfunction is usually temporary, it is associated with higher mortality after SAH. Takotsubo cardiomyopathy, also referred to as left apical ballooning, is a transient, virtually global LV dysfunction characterized by apical and mid-ventricular akinesia with relative sparing of the basal segment. It may occur as a response to sudden physical or emotional stress, when it generally has a benign prognosis, but it is also a rare cause of ventricular dysfunction after SAH, when it is associated with increased mortality.[16]

Neurogenic stunned myocardium may be associated with minimal clinical effects but, in severe cases, can lead to cardiogenic shock and pulmonary edema. Cardiovascular dysfunction often resolves spontaneously after a variable period, emphasizing the importance of general supportive intensive care during periods of instability. Modification of the sympathetic response might limit cardiac dysfunction after SAH and patients on chronic antihypertensive therapy have a lower incidence of SAH-associated cardiac injury. However, there is no strong evidence to recommend this line of therapy and, in any case, the risk of hypotension is a cause for concern. Inotropic support with dobutamine and, less so, milrinone is beneficial in the setting of low cardiac output, despite a mechanism of action similar to the cause of cardiac injury. Pure vasopressors are often necessary to maintain cerebral perfusion but their adverse effects on cardiac work risks potentiating myocardial injury. Characterizing cardiac

by mansdocs.com

performance using echocardiography and continuous cardiac output monitoring may be useful in guiding therapy in patients with symptomatic NSM.

Neurogenic pulmonary edema (NPO) and pneumonia are common after SAH and associated with adverse outcome. The mechanism of NPO is controversial but likely to be related to neurogenic-mediated catecholamine release that leads to both hydrostatic and permeability edema. Many patients with SAH and acute lung injury can be managed safely using lung protective ventilation strategies, but in others there can be a conflict between treating the lungs and the injured brain. A ventilation strategy that maximizes oxygenation while balancing risks to the lungs and injured brain should be identified individually for each patient.[17]

Dysnatremia

Hyponatremia after SAH is often related to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), although the cerebral salt wasting (CSW) syndrome and iatrogenic hemodilution can be implicated. As plasma tonicity reduces, fluid shifts may precipitate cerebral edema and neurological sequelae. SIADH occurs because of excess antidiuretic hormone secretion, causing water retention, volume overload and dilutional hyponatremia. CSW on the other hand is associated with raised atrial and brain natriuretic peptide and excessive renal sodium and water loss, leading to circulating volume contraction. It is important to distinguish between SIADH and CSW syndrome since the treatment of the two is diametrically opposed. Electrolyte-free water restriction, initially to 1,000–1,500 mL/day, forms the usual mainstay of treatment of SIADH but this may worsen cardiovascular instability and increase the risk of cerebral hypoperfusion after SAH. Consideration should be given to the use of hypertonic saline (1.8%) in hyponatremic patients with a high risk of DCI. Pharmacological therapies, such as demeclocycline and antidiuretic hormone (ADH)-receptor antagonists, may have a place in some patients. The primary treatment of CSW syndrome is volume and sodium resuscitation. Fludrocortisone or hydrocortisone may also be used to limit the natriuresis, but care must be taken to monitor for hypokalemia and hyperglycemia. Hypernatremia independently increases the risk of adverse cardiac outcome and death after SAH and patients with hypernatremia should be monitored for evidence of cardiac dysfunction.[18]

Fever

Fever occurs in up to 70% of patients, is more common in poor grade SAH and associated with worse outcome. While an infective cause should be excluded (pneumonia is particularly common), the fever can be related to the hypothalamic effects of subarachnoid blood. Paracetamol is first line therapy for fever control and although active cooling to normothermia has been associated with improved outcome, the adverse effects of shivering might offset its benefits.[19]

Glycemic Control

Hyperglycemia is common after SAH, occurring in around 30% of patients, and is associated with adverse outcome. Tight glycemic control is not recommended since it can be associated with increased cerebral metabolic crises. Current practice has adopted more relaxed glycemic targets (typically 6–11 mmol/L) limiting overly aggressive insulin administration and minimizing the risk of hypoglycemia and its known adverse effects on the injured brain.[20]

Anemia

Anemia is very common and associated with poor outcome after SAH, although transfusion itself is similarly associated with adverse outcome effects. In majority of cases it is due to hemodilution as a part of Triple-H therapy (hypervolemia, hemodilution and hypertension), still being used for treatment of cerebral vasospasm, or in cases where major blood loss in intraoperative period. Current guidance recommends that packed red cells be administered to maintain hemoglobin concentration between 8–10 g/dL, although higher thresholds might be appropriate in patients at high risk of DCI.[21]

Deep Venous Thrombosis

Sequential compressive devices (SCDs) should be used routinely in patients before definitive aneurysm treatment unless a contraindication exists such as preexisting deep venous thrombosis. After securing aneurysm either subcutaneous heparin (5,000 U SC TID) or low molecular weight heparin (40 mg SC daily) is more effective at preventing deep vein thrombosis than SCDs alone.[15]

REFERENCES

1. Ropper AH. Textbook of Neurology and Neurosurgical Intensive Care, 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2004.

by mansdocs.com

2. Caplan JM, Colby GP, Coon AL, et al. Managing subarachnoid hemorrhage in the neurocritical care unit. Neurosurg Clin N Am. 2013;24(3):321-37.
3. Smith M. Intensive care management of patients with subarachnoid hemorrhage. Curr Opin Anaesthesiol. 2007; 20(5):400-7.
4. Fugate JE, Rabinstein AA. Intensive care unit management of aneurysmal subarachnoid hemorrhage. Curr Neurol Neurosci Rep. 2012;12(1):1-9.
5. Spiotta AM, Provencio JJ, Rasmussen PA, et al. Brain monitoring after subarachnoid hemorrhage: lessons learned. Neurosurgery. 2011;69(4):755-66.
6. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-17.
7. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007;(3):CD000277.
8. Treggiari MM, Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Hemodynamic management of subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):329-35.
9. Pierot L, Aggour M, Moret J. Vasospasm after aneurysmal subarachnoid hemorrhage: recent advances in endovascular management. Curr Opin Crit Care. 2010;16(2):110-6.
10. Suarez JI, Participants in the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Magnesium sulfate administration in subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):302-7.
11. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011;10(7):618-25.
12. Dorhout Mees SM, van den Bergh WM, Algra A, et al. Antiplatelet therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007;(4):CD006184.
13. Wurm G, Tomancok B, Nussbaumer K, et al. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. Clin Neurol Neurosurg. 2004;106(2):97-103.
14. Lanzino G, D'Urso PI, Suarez J, et al. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;15(2):247-56.
15. Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage: new strategies for prevention and management. Curr Opin Crit Care. 2006;12(2): 78-84.
16. Nguyen H, Zaroff JG. Neurogenic stunned myocardium. Curr Neurol Neurosci Rep. 2009;9(6):486-91.
17. Muroi C, Keller M, Pangalu A, et al. Neurogenic pulmonary edema in patients with subarachnoid hemorrhage. J Neurosurg Anesthesiol. 2008;20(3):188-92.
18. Tisdall M, Crocker M, Watkiss J, et al. Disturbances of sodium in critically ill adult neurologic patients: a clinical review. J Neurosurg Anesthesiol. 2006;18(1):57-63.
19. Scaravilli V, Tinchero G, Citerio G. Fever management in SAH. Neurocrit Care. 2011;15(2):287-94.
20. Schmutzhard E, Rabinstein AA. Spontaneous subarachnoid hemorrhage and glucose management. Neurocrit Care. 2011;15(2):281-6.
21. Kramer AH, Gurka MJ, Nathan B, et al. Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage. Crit Care Med. 2008;36(7):2070-5.

by mansdocs.com

CHAPTER 40

Intensive Care Management of Postoperative Neurosurgical Patients

Mukesh M Gupta

INTRODUCTION

Appropriate neurocritical care is fundamental to the success of neurosurgical interventions to the brain and spinal cord. Great technical advances in operative procedures have made lesions previously considered inoperable now treatable, and advances in anesthesia have led to an increased number of operative procedures in both elderly and critically ill patients. The result of a technically perfect operation can be ruined by inadequate postoperative care. A complex operative procedure requires expert intensive care to correct abnormalities in homeostatic mechanisms, ensure adequate cerebral perfusion and oxygenation, and promote recovery of brain function. The complex interaction between the central nervous system (CNS) and systemic functioning requires intimate knowledge of both general intensive care and cerebral and spinal pathophysiology. Anticipation and early response prior to the full blown development of complications are hallmarks of good neurocritical care.

LOCATION AND DURATION OF POSTOPERATIVE NEUROCRITICAL CARE

Postoperative neurosurgical patients accounts for a large number of neurological intensive care unit admission and in many centers there is a flexible relationship between neurosurgery recovery and neurosurgical ICUs. Recovery time and location of postoperative care depends on the neurosurgical procedure, underlying premorbid conditions, anesthetic risk and expected postoperative neurological status. An admission policy for postoperative neurosurgical patients both in terms of location or duration varies widely between countries and centers and even within centers. Patients undergoing intracranial procedures are advised to stay for at least 24 hours in a specialized and designated recovery area. Following extracranial surgery, patients typically stay for shorter period. In these patients recovery duration prolonged only, if they have any complex neurosurgical procedure, long duration surgery, any intraoperative event, delayed recovery due to anesthesia and postoperative pain or vomiting or any hemodynamic swing in either direction. Neurointensive care protocols are required to ensure safe and adequate duration of recovery facility provision for these different categories of patients.

POSTOPERATIVE ANESTHESIA CONSIDERATIONS

The Neuroanesthetist aims to optimize the anesthetic technique for each patient so that, upon completion of surgery, a prompt and smooth recovery of conscious level is achieved. This allows neurological assessment and the detection of intracranial or spinal cord complications at the earliest opportunity. When surgery has been conducted without general anesthesia, or under sedation, a similar level of care provision is needed.

In general, the neurosurgical patient's trachea can be extubated as soon as his or her cardiovascular system is stable and ventilation is adequate. In general, unless there are extenuating circumstances (e.g. a history of gastrointestinal reflux), extubation is performed under deep anesthesia to prevent coughing, which will increase intracranial pressure. A head-up position at the time of extubation improves cerebral venous drainage and

by mansdocs.com

Table 1: Postoperative complications.

Systemic complications	*Neurosurgical complications*
• Coagulation disorders (blood loss, disseminated intravascular coagulation, drug induced)	• Postoperative hematoma (subgaleal, epidural, subdural and intraparenchymal)
• Thromboembolic (DVT, pulmonary embolism, myocardial infarction)	• Cerebral ischemia (subarachnoid hemorrhage, vasospasm, vessel occlusion)
• Pulmonary (atelectasis, pneumothorax)	• Brain swelling (edema, vasodilation)
• Hypovolemia (insufficient perioperative hydration, major blood loss)	• Infection (meningitis, subdural empyema, cerebral abscess)
• Infection (pneumonia, urinary tract infection, catheter sepsis)	• Seizures (infection, depressed compound skull fracture, cortical lesions)
• Metabolic (hyperglycemia [steroid induced], diabetes insipidus, hyponatremia)	• Hydrocephalus (obstruction/resorption)
• Air embolism (sitting position, opening of large cerebral veins during surgery)	• Tension pneumocephalus, CSF fistula
• Pressure sores and decubitus ulcers (intraoperative positioning, cervical traction, paraplegia)	• Inverse cerebellar herniation, cranial nerve lesions

(DVT: Deep venous thrombosis).

ventilatory function. On occasion, the neuroanesthetist may opt for a period of postoperative ventilation and sedation in the intensive care unit. Broadly, this occurs if patient ability to maintain the airway postoperatively is in doubt (e.g. following posterior fossa surgery when bulbar function may be compromised) or when level of consciousness is likely to be depressed following the procedure and there is a high risk of precipitating catastrophic intracranial hemorrhage or cerebral edema during emergence.

GOALS OF POSTOPERATIVE NEUROSURGICAL CARE

The principal goal of postoperative neurosurgical intensive care is early detection and treatment of postneurosurgical complications. The next is preventing systemic second insults that may initiate or exacerbate secondary damage in a vulnerable CNS. Consequently, priorities are to ensure adequate monitoring facilities, which may in the sedated and ventilated patient require further invasive monitoring of the intracranial system, and to ensure adequate oxygenation and perfusion of the brain. Postoperative complications may be systemic or neurosurgical (Table 1).

PREVENTION AND MANAGEMENT OF SYSTEMIC COMPLICATIONS AFTER NEUROSURGERY

The prevention and management of systemic complications after neurosurgical procedures follows general principles of "intensive care" medicine. It is, however, important to realize that systemic complications and second insult may initiate or aggravate cerebral damage. Aggressive treatment aimed at preventing and limiting second insult is of paramount importance. The main second insults, their causes, and adverse effects on brain homeostasis and function are summarized in Table 2, further illustrating the complex interactions between systemic events and CNS function. Conversely, CNS events may induce systemic derangement.

Cardiac Dysfunction

Electrocardiographic (ECG) abnormalities usually diffuse ST-segment changes mimicking cardiac ischemia and cardiac arrhythmias and left ventricular dysfunction may be caused by subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), or raised ICP. The mechanisms underlying of cardiac dysfunction is still unclear; but a sudden central sympathetic discharge following acute neurological insult has been observed. Most of these changes are benign and self-limiting.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema has been described early in the postoperative period after a variety of neurosurgical procedures, including brain tumors cysts, hydrocephalus, intracranial hemorrhages, and brainstem lesions. Although an infrequent event, this is potentially life threatening and requires rapid evaluation and emergent therapy in the ICU. Generally this complication appears in the initial 4 hours after the neurologic event. The mechanisms

by mansdocs.com

Table 2: Systemic secondary insults.

Event	*Main Causes*	*Adverse effects*
• Hypoxemia	• Hypoventillation • Aspiration/Atelectasis • Pneumonia • Anemia	• Decreased O_2 delivery and increased risk of ischemic damage
• Hypotension	• Hypovolemia • Cardiac failure • Sepsis • Neurogenic shock	• Decreased CPP, decreased CBF, increased risk of ischemia
• Anemia	• Blood loss	• Decreased O_2 delivery, increased risk of ischemia
• Hypocapnia	• Hyperventilation (spontaneous or induced)	• Cerebral vasoconstriction with risk of ischemic damage
• Hypercapnia	• Respiratory depression	• Increased Cerebral Blood Volume, ↑ICP
• Hyperthermia	• Stress response • Infection • Central dysregulation	• Metabolic requirements > delivery
• Hypothermia	• Exposure • Central dysregulation	• Significant coagulaopathy, ↑ infection risk
• Hyperglycemia	• Hypothermia, steroids	• Acidosis, electrolyte disturbance, ↑ infection risk
• Hypoglycemia	• Inadequate nutrition, pituitary insufficiency	• Energy depletion, seizures
• Hyponatremia	• Hypotonic fluids • Cerebral salt wasting • Syndrome of inappropriate antidiuretic hormone	• Increased edema, seizures
• Hypernatremia	• Diabetes insipidus • Osmotic agents (3% NaCl)	• Lethargy, coma

(CPP: Cerebral perfusion pressure; CBF: Cerebral blood flow; ICP: Intracranial pressure).

underlying this condition are unclear; a sudden central sympathetic discharge may trigger pulmonary venoconstriction, systemic arterial hypertension, increased left ventricle afterload, increased capillary permeability in the pulmonary vascular bed, and simultaneously cause cardiac ischemia and ventricular failure. Treatment is supportive therapies directed at intracranial hypertension, opioids and sedatives to control sympathetic activity, mechanical ventilation with positive end-expiratory pressure (PEEP) and diuretics.

Hypercoagulopathy and Thrombosis Prophylaxis

Deep venous thrombosis (DVT) has been reported to occur in 18–50% of neurosurgical cases and pulmonary embolism (PE) in 0–25%. Release of factors from damaged brain tissue may induce local and systemic transient hypercoagulopathy in immediate postoperative period. Options for prevention of thrombosis prophylaxis in neurosurgical patients include both mechanical (graduated compression stockings, intermittent pneumatic compression stockings) and pharmacologic (low dose of classic heparin and low molecular weight heparin) therapies. Intuitively, mechanical therapies carry less associated risk, but pharmacologic approaches are more effective in preventing thrombotic complications. In addition, early mobilization in the postoperative phase, whenever possible, is recommended.

PREVENTION AND MANAGEMENT OF POSTOPERATIVE NEUROSURGICAL COMPLICATIONS

Any change in conscious level, pupillary response or the development of focal neurological signs requires urgent CT scanning; the patient's airway should be secured and all the precautions taken for an emergency induction of anesthesia.

Postoperative Brain Swelling

Modern neuroanesthesiology techniques have diminished the incidence of perioperative brain swelling. Nevertheless, significant swelling may sometimes occur, causing surgical difficulties and possibly critical problems

by mansdocs.com

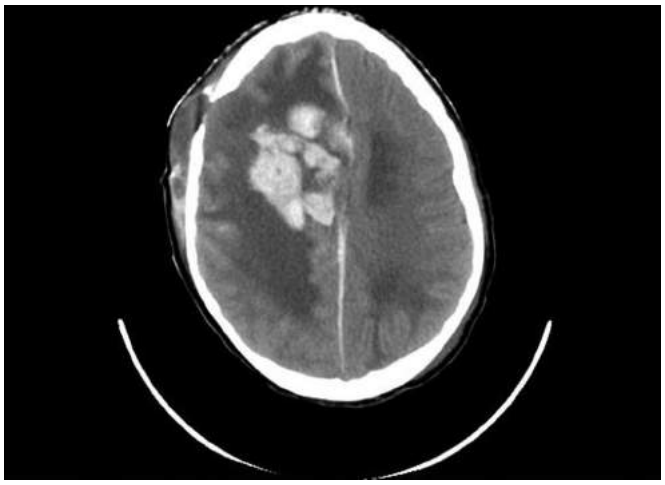


Fig. 1: Postoperative case of right posterior frontal tumor develop postoperative intraparenchymal hematoma with Perilesional cerebral edema.

in the ICU. Predisposing factors are hypercapnia, arterial hypertension, hyponatremia, obstruction of venous drainage, prolonged brain tissue retraction and silent or overt seizures during surgery or in the immediate postoperative phase. Urgent CT brain should be done to diagnose the reason of brain swelling. It is usually treated with correction of systemic or neurological derangements, dexamethasone and osmotic agents (Fig. 1).

Postoperative Intracranial Hematoma

Intracranial postoperative hemorrhage occurs in approximately 1% of procedures and mainly concerns intraparenchymal hematomas (43–60%), epidural hematomas (28–33%) and subdural hematomas (5–7%). The risk of intracranial hemorrhage increases with hypertension, coagulopathy, poor surgical hemostasis and chronic alcohol intake. Although it occurs most commonly within the first 6 hours following surgery, hematomas occurring later must be considered. The possibility of a postoperative hematoma should be considered in all patients who are not fully alert postanesthesia, as well as in those who exhibit secondary deterioration.

Hydrocephalus

The risk of obstructive hydrocephalus is high after posterior fossa surgery or when blood is present in the ventricular system causing obstruction. In cases with a high risk of postoperative hydrocephalus, an external ventricular drain (EVD) may be sited during the operation to allow CSF drainage and thus treat the raised intracranial pressure (ICP).

Seizures

Every intracranial operation carries a risk of seizure activity, but is probably greatest after cerebrovascular surgery (arterio-venous malformation (AVM), aneurysm), cerebral abscess and subdural empyema, convexity and parafalcine meningiomas and traumatic brain injury. Opinions vary on the need and duration of prophylactic anti-seizure therapy. Preoperative anticonvulsant medication should be continued throughout the perioperative period. If postoperative seizures occur, phenytoin is generally the anticonvulsant of choice.

Tension Pneumocephalus

During intraoperative period, air accumulates in the intracranial compartment especially during posterior fossa surgery in sitting position due to continuous cerebrospinal fluid (CSF) drainage and may lead to a tension pneumocephalus or pneumoventricle. In immediate postoperative period present with clinical symptomatology including decreasing level of consciousness, signs of raised ICP, and seizures. Generally, pneumocephalus resolves gradually and do not require specific treatment but may need needle aspiration of air.

MONITORING DURING THE POSTOPERATIVE PERIOD

Specific care and monitoring of the postoperative neurosurgical patient requires accurate knowledge of the preoperative condition and the intraoperative procedure, including the surgery, anesthesia, and any surgical complications or difficulties. Pertinent aspects are summarized in Table 3.

The intensity of monitoring depends on the complexity of the neurosurgical procedure and any underlying premorbid condition. A high degree of clinical vigilance is required for the earliest identification of surgical complications. Intensive care monitoring includes clinical evaluation, technical monitoring, and follow-up CT or magnetic resonance imaging (MRI). Various approaches to monitoring are summarized in Table 4.

Respiratory Monitoring

Any decline in conscious level (as measured by the Glasgow Coma Scale), results in diminished airway reflexes. Generally, patients with a GCS of less than or equal to 8 cannot protect their airways; similarly, those patients with

by mansdocs.com

Table 3: Postoperative admission review in neurosurgical ICU after neurosurgical operations.

• Preoperative clinical status	• Neurologic deficit (level of consciousness, focal paresis, cranial nerve lesions, hormonal deficits) • Pre-existing disease (especially pulmonary and cardiac) • Preoperative medication • Presenting complaints • Allergy
• Intraoperative course (neuroanesthesia)	• Narcotic agents • Blood loss and substitution • Intraoperative investigation • Intraoperative secondary insults.
• Intraoperative course (neurosurgical)	• Indication, approach, and duration of surgery • Surgical position • Surgical difficulties and complications (brain swelling, difficult hemostasis, temporary or definite vascular occlusion, opening of air sinus) • Immobilization/positioning of patient
• Postoperative instructions	• Postoperative medication (e.g. anticonvulsants, antibiotics, steroids, mannitol, thrombo-prophylaxis prophylaxis) • Instructions for postoperative care and monitoring • Instructions for removal of drainage, tubes and stitches • Preferred duration of postoperative mechanical ventilation • Instructions for follow-up CT or MRI examination (if indicated)

Table 4: Postoperative monitoring after neurosurgery.

• Clinical monitoring	• Level of consciousness (Glasgow Coma Scale), pupillary reactivity, focal deficits, cranial nerve lesions
• Systemic monitoring	• Electrocardiogram and heart rate, respiration, pulse oximetry, end-tidal CO_2, blood pressure (invasive, noninvasive), temperature, central venous pressure, Swan Ganz catheter
• Brain-specific monitoring	• Intracranial pressure and cerebral perfusion pressure, jugular oximetry, brain oxygen tension monitoring, microdialysis, transcranial doppler, electroencephalogram, evoked potentials
• Catheters and tubes monitoring	• Central or peripheral venous catheter, arterial catheter, urinary catheter, gastric tube, tracheal tubes, surgical drains
• Laboratory examinations	• Blood gases, hematology, electrolytes, glucose and on indication coagulation status
• Imaging examinations	• Chest radiograph • Computed tomography or magnetic resonance imaging follow-up (as required)

lower cranial nerve dysfunction (e.g. after posterior fossa surgery) are at risk. Airway obstruction may occur following surgery in the neck (e.g. carotid artery surgery, anterior cervical decompression) with obstructive hematoma, soft tissue swelling and vagal nerve injury. Vagus nerve dysfunction may also occur following operative procedures for movement disorders. Trans-sphenoidal surgery may give rise to bleeding and blood clots in the airway, whereas tran-soral procedures may cause macroglossia and oral edema. A "difficult airway" may be created by occipito cervical spine fixation, especially when combined with transoral surgery. In these cases, either extubation is delayed until tissue airway improved or tracheostomy, if prolonged need of airway assistance is required.

Respiratory control may be impaired as a result of residual effects of anesthesia, posterior fossa surgery or brainstem compression. Clinically, this may manifest as irregular patterns of breathing or periods of apnea. Arterial carbon dioxide tension must be monitored carefully; significant rises will result in increases in cerebral blood volume and ICP. Respiratory mechanics will be compromised following high spinal cord injuries, or with some underlying neuromuscular diseases (e.g. severe muscular dystrophies). If the forced vital capacity (FVC) is less than 20 mL/kg, admission to an intensive care unit is indicated, and when FVC less than 15 mL/kg tracheal intubation and ventilatory support is often necessary.

Neuromuscular blockade needs to be fully reversed. A significant percentage of patients returning from the operating theatre have residual effects of nondepolarizing neuromuscular blockade with consequent reduced respiratory reserve. Continuous positive airway pressure (CPAP)

by mansdocs.com

and noninvasive nasal ventilation may be necessary in patients with reduced ventilatory capacity, but both modes of support are contraindicated if the surgical wound involves the nasopharynx, with potential continuity with the intracranial space (e.g. after trans-sphenoidal surgery).

Cardiovascular System

Postoperative hypertension must be avoided to minimize the risk of precipitating an intracranial hemorrhage or increasing cerebral edema by exceeding the local limit of autoregulation. It is therefore usual to continue invasive arterial monitoring during the recovery period. Common causes of systemic hypertension in the postoperative phase include pain, bladder distension, shivering and hypercarbia. Hypertension may also be a result of raised ICP and can precede a fall in conscious level and heart rate (as part of the Cushing reflex). Strict arterial blood pressure limits are often required following aneurysm surgery or coiling to optimize cerebral perfusion. Limits depend on premorbid blood pressure, whether the aneurysm has ruptured and whether it is protected (coiled or clipped) or unprotected. Manipulation of BP with use of vasopressors (e.g. norepinephrine) or hypotensive agents (e.g. labetalol) may be necessary to achieve predetermined goals.

Neurological Monitoring

Neurological observations should include Glasgow coma scale (Table 5), cranial nerve function, limb power and sensation, and pupillary responses. The exact emphasis or observation will depend on the nature of the surgery. Causes of neurological deterioration are numerous, including intracranial hemorrhage or edema, obstructive hydrocephalus, fluid and electrolyte imbalance (especially hyponatremia), hypoglycemia, hypoxemia, sepsis and seizures. Impaired bulbar function may occur following posterior fossa surgery and basal skull surgery; it may also occur in patients with underlying neuromuscular disorders. Cranial nerves (especially VII, VIII, IX, X and XII) should be monitored carefully in these cases. A continuous reappraisal of airway protection is necessary and, if bulbar function is found to be impaired, admission to an intensive care unit and tracheal intubation is the management of choice. Failure to recognize this complication usually results in the patient developing aspiration pneumonia. In patients with swollen brainstem areas, the impaired bulbar function may precede deterioration in autonomic function or vital centers.

Table 5: Glasgow coma scale.

Eye opening	*Motor response*	*Verbal response*
1. None	1. None	1. None
2. To pain	2. Abnormal extension	2. Incomprehensible (groaning) sounds
3. To speech	3. Abnormal flexion	3. Inappropriate words
4. Spontaneous	4. Flexion (withdrawal)	4. Disoriented, confused
	5. Localizing	5. Oriented
	6. Obeying commands	

Temperature Monitoring

Temperature monitoring is also important, since hypothermia can depress neurologic function to the point of obtundation or coma. Conversely, fever, by increasing metabolic requirements, may exacerbate secondary injury.

Intracranial Pressure Monitoring and Cerebral Perfusion Pressure

Intracranial pressure (ICP) monitoring is principally indicated in severe traumatic brain-injury, but can be useful in poor-grade patients with aneurysmal subarachnoid hemorrhage (SAH) and postoperative patient who are at risk of increase brain swelling. Relatively few data exist on routine ICP monitoring in the postoperative period. ICP monitoring carries a 0.5% risk of hemorrhage and a 2% risk of infection depending on site and duration of monitoring. Intraventricular catheters are preferable because they are accurate, can be recalibrated, and allow drainage of CSF. Intraparenchymal probes are user friendly and accurate. Less accurate data are provided by subdural catheters and epidural probes are unreliable. Cerebral perfusion pressure (CPP) can be calculated by mean arterial blood pressure (ABP) and ICP by simple formulae.

CPP = MAP - ICP

Cerebral Blood Flow Monitoring

Recent years have seen great advances in approaches to monitoring cerebral blood flow (CBF) and CBF-related variables, particularly in the field of neuroimaging. Both CT and MRI techniques have been developed for perfusion imaging and angiography, and possibilities for determining areas of the brain at risk for ischemia are now routinely available to the clinician. These approaches have replaced measurements of CBF with stable xenon CT scanning. Transcranial Doppler (TCD) provides a noninvasive

by mansdocs.com

assessment of blood flow velocity through the basal cerebral arteries. TCD is widely used for the detection and tracking of cerebral vasospasm, but various studies have shown a disappointing correlation when measured flow velocities are compared with direct measurements of CBF.

Cerebral Oxygenation and Metabolism

Three approaches to monitoring cerebral oxygenation are available to the clinician: jugular bulb oximetry ($Sjvo_2$), noninvasive cerebral oximetry ((i.e. near-infrared spectroscopy [NIRS], rSo_2 (somanetics) or tissue index of oxygenation (Hamamatsu)) and cerebral parenchymal oximetry monitors (LICOX- $PbrO_2$).

Microdialysis

The technique of microdialysis allows for measurement of substrate and metabolites (glucose, lactate, pyruvate), amino acids (glutamate), as well as indicators of cerebral damage (glycerol or other proteins as tau and beta amyloid) in the extracellular fluid of the brain. Microdialysis is employed in various specialized neurointensive care units, mainly for research purposes.

Electroencephalogram (EEG) Monitoring

Continuous EEG (cEEG) monitoring has the potential for detecting nonconvulsive status epilepticus in ICU patients. Electroencephalographic bispectral analysis (BIS) may be useful in assessing the level of sedation in neurocritical care patients.

POSITIONING OF THE PATIENT IN THE POSTOPERATIVE PERIOD

After craniotomy patients should be placed at 30° head-up for optimal ICP management. However, patients who have undergone evacuation of chronic subdural hematoma should avoid excessive head up positioning as there is an increased risk of re-bleeding. Following trans-sphenoidal surgery, patients benefit from being in head up as soon as possible, whereas those who have had lumbar surgery or those who have a cerebrospinal fluid (CSF) leak will benefit from being kept in a horizontal position.

POSTOPERATIVE ANALGESIA

Analgesic management should allow rapid recovery and accurate neurological assessment, while ensuring the patient's comfort and avoiding any potentially catastrophic increase in systemic hypertension. Scalp infiltration decreases postoperative pain scores for only the first 2 hours after craniotomy. Regular paracetamol should be administered, usually in combination with regular opioid medication. Nonsteroidal anti-inflammatory drugs are avoided in the immediate postoperative period following intracranial surgery because of their effect on platelet function. Chronic pain medications taken preoperatively are usually continued in our practice. Neuropathic and postsurgical pain may be modified by the use of gabapentin.

POSTOPERATIVE FLUID MANAGEMENT

Blood–brain barrier impairment may follow intracranial surgery and in this situation derangements in water and electrolyte balance may rapidly cause disorientation, alter Glasgow coma scale (GCS) and induce seizures. Fluid losses should be replaced with judicious volumes of isotonic or hypertonic fluids as hypotonic solutions can increase the risk of cerebral edema. Furthermore, glucose solution can result in hyperglycemia, which may worsen any ischemic insult. Pituitary dysfunction can occur with subarachnoid hemorrhage, skull fractures, craniofacial trauma, and hypothalamic/pituitary surgery. Diabetes insipidus is not infrequent and suspicion of this complication should be raised if the hourly urine output is more than 200 mL/hour, is of a low urine specific gravity (< 1.005) and is accompanied by an increased plasma osmolality and extreme thirst. If confirmed by urine and plasma osmolalities, desmopressin is the treatment of choice with close monitoring of fluid balance and plasma sodium levels.

NEUROSURGICAL INTENSIVE CARE UNIT DISCHARGE CRITERIA

After appropriate postoperative care in neurointensive care unit, patient can be shifted to ward. However, before safe transfer is considered, a number of criteria must be met. The patient must have a patent airway with protective reflexes present, oxygen saturations maintained above 95% or an appropriate level, with oxygen as prescribed. Breathing must be spontaneous and regular, pulse and blood pressure within normal levels for the patient (with reference to preoperative observations), and invasive arterial monitoring and unnecessary venous catheter removed prior to shift out. Neurologically, the patient must have an appropriate GCS assessment, with no acute reduction

by mansdocs.com

or asymmetry in limb motor power, and no new or unexplained pupillary changes. Any EVD or lumbar drain present should be placed at the required level as documented by the neurosurgeon, and the volume to be drained noted. The wounds should be dry and dressed, drains if possible remove them. Review medications, diet and fluids before shifting patient to neurosurgical ward.

CONCLUSION

Postoperative neurosurgical patients present unique challenges to the caregivers. The rapidity with which neurologic injury can occur, and the devastating consequences of such injury, requires constant vigilance as well as diligence to perform timely evaluations and aggressive treatments. Many postoperative complications can be avoided, or their morbidity lessened, with quality neurocritical care.

BIBLIOGRAPHY

1. Bhatia A, Gupta AK. Neuromonitoring in the intensive care unit. Intracranial pressure and cerebral blood flow monitoring. Intensive Care Med. 2007;33(7): 1263-71.
2. Cottrell JE, Young WL. Cottrell and Young's neuroanesthesia, 5th edition. Philadelphia: Elsevies Medical Sciences; 2010.
3. Ropper AH, Green Dr, Diringer MN, et al. Neurological and Neurosurgical Intensive Care, 4th edition. Lippincot Williams and Wilkins; 2004.

by mansdocs.com

SECTION 7

Obstetric Critical Care

by mansdocs.com

by mansdocs.com

CHAPTER

41

Physiology of Pregnancy

Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

INTRODUCTION

Pregnant patients in intensive care unit (ICU) differ from other patients, due to complex physiological changes of pregnancy and unique obstetrics problems (Table 1). While managing these patients, intensivists have to take care of two lives, match up with the physiological changes and treat obstetric problem as well. In this article, we give an overview of the critical illnesses that afflict the obstetric patient. 100–900 per lakhs gestation may need ICU care. This depends on age, socioeconomic status, country (developing vs developed), maternal medical co-morbidity and antenatal care. There are certain obstetric complications which bring the patient in ICU while certain medical conditions complicate the pregnancy and bring the patient in ICU. A combination of good antenatal care, early detection and intervention in complicated pregnancies, and timely delivery (by cesarean delivery, if necessary) has reduced the maternal mortality rate in developed countries to 4–20 per 100,000 deliveries. On the other hand, maternal mortality rate is high in developing countries. Inadequate medical and surgical facilities, lack of antenatal care, high costs of treatment, social bias, and traditional customs hamper proper implementation of maternal health programs. High-quality neonatal intensive care is not available or is available only in large cities. Consequently, the neonatal mortality rate associated with elective premature delivery is high, and pregnant women with conditions like severe preeclampsia often refuse elective preterm delivery, exposing themselves to a high risk of organ dysfunction and possibly death. As a result, although pregnancy-induced hypertension is less common in Asian Indians than in Whites and its complications (e.g. eclampsia and renal failure) are common in South Asians but rare in Americans, Canadians and Europeans.

Table 1: Conditions unique to pregnancy nonobstetric causes.

Obstetric hemorrhage	
• Placental abruption	• Respiratory failure
• Preeclampsia/eclampsia HELLP syndrome (HELLP is an abbreviation of the main findings: hemolytic anemia; elevated liver enzymes and low platelet count)	• ARDS • Acute renal failure
• Acute fatty liver of pregnancy	• Urinary tract infection
• Chorioamnionitis amniotic fluid embolism	• Diabetic ketoacidosis
• Puerperal sepsis Intrauterine death	• Preexisting medical conditions
• Peripartum cardiomyopathy	• Sepsis
• Pulmonary embolism	• Viral infection/reactivation

Literature is sparse regarding the mechanisms whereby pregnant women develop critical illness. Pregnant women have been excluded from most large physiological studies and therapeutic trials in critical care. Patients with primary obstetric disorders tend to have a better overall prognosis as delivery of the fetus usually reverses the illness and resuscitations more effective. Preterm babies also have chance of survival in hospitals with established neonatal ICUs.

by mansdocs.com

PHYSIOLOGICAL CHANGES DURING PREGNANCY AND ITS RELEVANCE IN ICU CARE OF OBSTETRIC PATIENTS

Pregnancy is characterized by progesterone-mediated hyperemia and edema of mucosal surfaces. Pregnant women tend to have more nasal congestion. Accordingly, endotracheal and nasogastric tube size should be downsized. The diaphragm is displaced cephalad about 4 cm, and the lower chest wall widens about 5–7 cm. This upward movement of the diaphragm is important to consider when placing a chest tube in the ICU. At 12 weeks, the bladder becomes an abdominal structure and is more susceptible to blunt trauma. At 20 weeks, the fundus of the uterus is at the level of the umbilicus and can be injured directly in blunt or penetrating trauma.

RESPIRATORY CHANGES

Spirometry remains normal throughout pregnancy. Flow volume loops, and peak flows remain unchanged. Total lung capacity decreases by about 4–5%. This change mostly is caused by the upward displacement of the diaphragm. Functional residual capacity (FRC) decreases by 20% because of decreases in expiratory reserve volume and residual volume. The changes in minute ventilation during pregnancy are shown in Figure 1.

This may remain the same or increase slightly in early pregnancy and subsequently return to normal values. Ventilation and oxygen consumption are the major parameters that change during pregnancy. Minute ventilation increases by about 50% during pregnancy, mostly because of increased metabolic rate, changes in the mechanics of breathing and increases in progesterone level. The increase in minute ventilation leads to a normal hyperventilation of pregnancy, which in turns leads to a mild chronic respiratory alkalosis with a compensatory metabolic acidosis. A normal arterial blood gas in a gravid woman is a pH of 7.40–7.47, with a $PaCO_2$ of 30–32 mm Hg and a normal to slightly elevated PaO_2. The kidneys compensate partially for the alkalosis by increasing renal bicarbonate excretion, which keeps serum HCO_3 levels between 18 mEq/L and 21 mEq/L. Arterial blood gas values of 7.47 for pH, 32 mm Hg for $PaCO_2$, and 19 mEq/L for HCO_2 do not necessarily requires further evaluation. The combination of the decrease in FRC and the increase in oxygen consumption lowers maternal oxygen reserve and increases chance of hypoxemic injury. One should be ready for this problem and difficult airway while managing airway in pregnant patients.

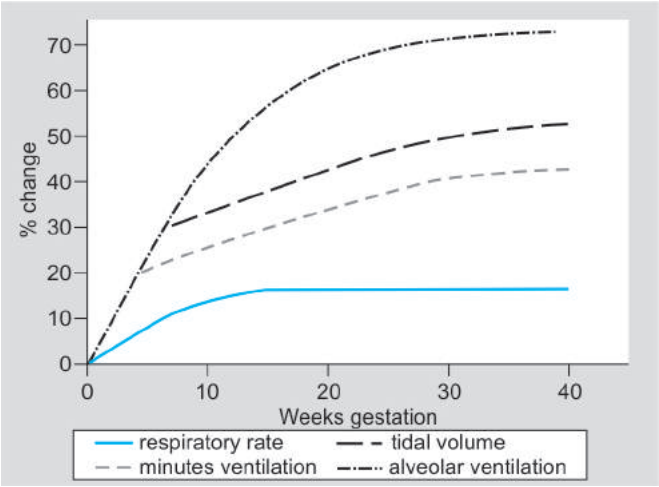


Fig. 1: Respiratory changes during pregnancy.

CARDIAC CHANGES

Maternal cardiac output begins to increase at about 6 weeks' gestation. Maternal blood volume increases progressively during pregnancy by about 30–50% more than the volume during the nongravid state. Maternal red cell mass increases only 20–30%, which results in hemodilution. The increase in blood volume of 1,000–1,500 mill partially offsets peripartum blood loss.

As the uterus enlarges by about 20 weeks' gestation, the supine position may result in significant compression of the inferior vena cava, or supine hypotension syndrome. This uterine compression effectively may decrease venous return, resulting in a 20–30% decrease in ejection fraction. Lateral repositioning of the patient with a foam wedge or pillow placed under the right buttock can displace the uterus to the left, restoring cardiac output. This maneuver is important in the ICU during resuscitation of critically ill pregnant patients.

Echocardiography of normal pregnant patients demonstrates the following: increases in all cardiac chamber dimensions, increased left ventricular wall thickness, small pericardial effusions, mild tricuspid and pulmonic regurgitation in 90% of patients and mild mitral regurgitation in 30%.

RENAL CHANGES

By 16 weeks' gestation, the glomerular filtration rate increases by 50% and remains elevated throughout

by mansdocs.com

pregnancy. Creatinine clearance also increases, resulting in lower levels of serum creatinine, blood urea nitrogen, and uric acid. Plasma levels of keratinize and blood urea nitrogen that exceed 0.8 mg/100 mL and 14 mg/100 mL, respectively, may indicate renal impairment. Almost 60% of infants born to women with a serum creatinine level exceeding 1.4 mg/dL are premature.

FETAL PHYSIOLOGY

The care of pregnant patients in the ICU requires a formal understanding of the uteroplacental unit. The placenta serves the following three main functions: (1) respiratory and gas exchange, (2) nutrition for the fetus and (3) waste elimination. Maternal oxygen delivery to the placenta is affected by uterine artery blood flow, oxygen content of the uterine artery blood, and hemoglobin (Hb) concentration and saturation. Uterine blood flow at term is about 10% of cardiac output (600–700 mL/min), compared with 50 mL/min in the nonpregnant state.

Maternal Fetal Circulation

Hypotension, uterine contractions and vasoconstriction can decrease uterine blood flow (Fig. 2). Maternal hypotension can result from many situations in the ICU, including hypovolemia, sepsis, medication use and placement in the supine position. Vasoconstriction can be seen in preeclampsia and with administration of the many inotropic support agents that commonly are used in the ICU. Adrenaline, which has predominantly β-adrenergic activity, is the vasopressor of choice for the treatment of hypotension in pregnancy.

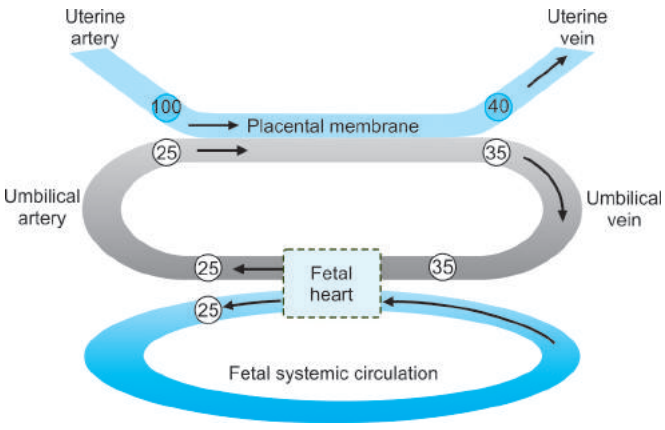


Fig. 2: Maternal fetal circulation.

The fetus has many protective mechanisms to ensure its oxygen extraction capacity. The fetus has a higher Hb concentration (15–16 g/dL). Fetal Hb is 80–90% saturated at a PO_2 of 30–35 mm Hg, whereas the major form of adult Hb is only 30% saturated at this PO_2. This differences a result of the leftward shift of the fetal oxygen dissociation curve. The fetus has the ductus arteriosus, which provides the fetus with two ventricles to supply circulation. Even though the fetal umbilical vein PO_2 is relatively low at 35 mm Hg, the fetal oxygen content is relatively high because of the higher Hb saturation and concentration. Increasing the fraction of inspired oxygen to the mother does not affect fetal PO_2 greatly. The fetus has about 42 mol of oxygen reserves, and its oxygen consumption is 20 mol/min (Table 2). In the face of complete hypoxia to the fetus, only 2 minutes of oxygen reserve would be expected; however, a fetus with this condition can survive at least 10 minutes by shunting blood flow to vital organs and decreasing oxygen consumption. In the setting of trauma-induced blood loss, maternal blood flow is maintained at the expense of the fetus.

ACID-BASE STATUS

Fetal acid-base measurements using scalp blood sampling may be used to further assess a fetus with an abnormal FHR pattern. The finding of a pH less than 7.2 is associated with significant physiological depression, while a normal fetal outcome can be expected with pH greater than 7.25. In the critically ill mother, maternal acid-base abnormalities may influence the measured fetal pH. Fetal acidosis may be masked in the hyperventilating patient who develops a respiratory alkalosis, and a low fetal pH may be found secondary to maternal acidosis without fetal compromise. In this situation the maternal-fetal pH difference may be valuable.

Table 2: Fetal oxygenation values.

Measurement	*Value*
Fetal umbilical vein PO_2	35 mm Hg
Fetal O_2 content	16.2 mL/dL
Fetal O_2 saturation 80% at PO_2	35 mm Hg
Fetal hemoglobin	16 g/dL
Fetal O_2 consumption	20 mL/min
Fetal O_2 stores	42 mL

Source: Data from Chesnutt AN, Matthay MA, DiFederico EM. Critical illness in pregnancy. Clinical Pulmonary Medicine. 1998;5:242.

by mansdocs.com

PLACENTAL GAS EXCHANGE

Introduction

Placenta is an inefficient gas exchange organ compared to that of lung and it is crucial for the critical care specialist to understand and know the mechanisms of gas exchange across placenta to maintain adequate fetal oxygenation. The uterine blood flow does not have autoregulation and placental blood flow is directly dependent on mean arterial maternal blood pressure.

Gas Exchange: Comparing Placenta with Lung

Gas exchange in the placenta is much less efficient than in a lung. This is because the minimum diffusion distance is much larger (e.g. 3.5 μm vs 0.5 μm in the lung) and the permeability of the blood-blood barrier is much lower than the permeability of the blood-gas barrier in the lung.

The total surface area of the placenta at term is about 16 m^2 as compared to 50–60 m^2 in the adult lung. The surface area is about a quarter of the size but it transfers only one-tenth of the oxygen. A relatively much larger surface area compensates for the inefficiency of the gas exchange.

In summary, as compared to the adult lung, the placenta is inefficient at gas exchange because of larger diffusion distance and lower gas permeability.

Mechanisms to Match Increased Fetal Requirements

The factors involved are:

- Increased maternal blood supply to the placenta (Uterine flow increases 20-fold during pregnancy)
- Increased fetal blood supply to the placenta
- Presence of fetal Hb which has a higher oxygen affinity than maternal HbA
- Higher Hb concentration in the fetus (40% higher than in adult)
- The Double Bohr Effect.

Uterine Blood Flow at Term and Fetal Blood Flow

About 500–750 mLs/min and 85% of this goes to the placenta. Note that the uterine supply to the placenta is not autoregulated and flow is pressure dependent. Umbilical arteries supply fetal deoxygenated blood to placenta.

The fetal cardiac output at term is about 1,000 mLs/min; from 25–55% of this goes to the placenta. It has a lower P50 (18–20 mm Hg) than adult Hb (26.6 mm Hg). This means fetal Hb has a *higher oxygen affinity* and this assists it to load oxygen in the placenta while maternal Hb is unloading oxygen. It has a higher saturation at a given pO_2 than adult Hb, e.g. fetal Hb has a saturation of 80% at a pO_2 of 30 mm Hg.

Fetal Hemoglobin Have Low P50

The higher P50 of adult Hb in red cells is due to the right shift that occurs in the presence of high levels of 2, 3-diphosphoglycerate (DPG) in the red cell. The 2, 3-DPG binds to the α-chains of Hb (especially *deoxy* HbA) to cause this effect. Several amino acids are involved in the binding and each tetramer of adult Hb binds one molecule of 2, 3 DPG.

Fetal Hb is a tetramer: $\alpha_2\ \gamma_2$. There are no β-chains so HbF is insensitive to a shift due to 2, 3 fetal Hb is a tetramer: $\alpha_2\ \gamma_2$. There are no β-chains so HbF is insensitive to a shift due to 2, 3-DPG binding.

At birth about 80% of the neonate's Hb is HbF. This decreases rapidly so that by the age of 6 months less than 5% of the baby's Hb is HbF. Only very small amounts of HbF are normally present in adults (<1% of total Hb in adults).

Double Bohr Effect

The term *double Bohr effect* refers to the situation in the placenta where the "Bohr effect" is operative in both the maternal and fetal circulations.

The increase in pCO_2 in the maternal intervillous sinuses assists oxygen unloading. The decrease in pCO_2 on the fetal side of the circulation assists oxygen loading. The Bohr effect facilitates the reciprocal exchange of oxygen for carbon dioxide.

The double Bohr effect means that the oxygen dissociation curves for maternal HbA and fetal HbF move apart (i.e. in opposite directions).

Special Factors Which Assist Carbon Dioxide Transfer Across the Placenta

The important factors relevant to the placenta are:

- Maternal hyperventilation results in a low maternal pCO_2 which increases the gradient favoring CO_2 transfer.
- A double Haldane effect occurs and this is unique to the placenta.
- *Hemoglobin at birth is typically high*: About 17–18 g/dL. Hb change in the 1st year after birth appears. The

by mansdocs.com

major changes are: Decrease in Hb (*physiological anemia of infancy*), rapid decrease then elimination of HbF (as discussed above), increased production of adult Hb (HbA) to replace HbF. After birth, the arterial pO_2 (and Hb saturation) in the neonate is much higher and erythropoietin levels consequently drop to undetectable levels. Red cell production is markedly decreased and Hb falls. The decrease in oxygen delivery is partially compensated by a shift of the Hb oxygen dissociation curve to the right as HbF is replaced by HbA and red cell 2, 3-DPG levels rise. Finally, Hb levels fall far enough to cause increased levels of erythropoietin and red cell production increases. The physiological anemia of infancy lasts for about 6 months.

pO_2, SO_2 and pCO_2 Values in the Uterine Vessels and in the Umbilical Vessels (Table 3)

Typical values are:

- *Maternal circulation:*
  - *Uterine artery*: pO_2 100 mm Hg (SO_2 98%); pCO_2 32 mm Hg
  - *Uterine vein*: pO_2 40 mm Hg (SO_2 75%); pCO_2 45 mm Hg.
- *Fetal circulation:*
  - *Umbilical artery*: pO_2 18 mm Hg (SO_2 45%); pCO_2 55 mm Hg
  - *Umbilical vein*: pO_2 28 mm Hg (SO_2 70%); pCO_2 40 mm Hg

Table 3: Maternal and fetal oxygenation parameters.

Mother	
1. Uterine blood flow	600 mLs/min
2. Maternal (Hb)	120 g/L (Low die "physiological anemia")
3. SO_2 in the uterine artery	98%
4. SO_2 in the uterine vein	75%
5. pO_2 in the uterine artery	100 mm Hg
6. pO_2 in the uterine vein	40 mm Hg
Fetus	
7. Umbilical blood flow	300 mLs/min
8. Fetal (Hb)	170 g/L
9. SO_2 in umbilical artery	45% (despite low pO_2 due high O_2 affinity)
10. SO_2 in umbilical vein	70% (despite low pO_2 due high affinity)
11. pO_2 in umbilical artery	18 mm Hg
12. pO_2 in umbilical vein	28 mm Hg

Oxygen Balance Across the Placenta

The points to consider are:

- Oxygen is delivered to the placenta from the maternal uterine artery and the fetal umbilical artery
- Oxygen is taken away from the placenta in the uterine vein and the umbilical vein.

Placental oxygen consumption is large and is equal to the difference between the oxygen delivered to the placenta and the oxygen taken away from the placenta. Placental oxygen consumption is about 10 mLs/kg/min. The placenta is typically one-seventh the weight of the fetus so placental oxygen consumption is about 5 mLs O_2/min.

Fetal oxygen consumption at term is almost 5 mLs O_2/kg/min or a total of about 15–17 mLs O_2/min. It is equal to the difference between the oxygen delivery to the fetus in the umbilical vein and the oxygen return to the placenta in the umbilical artery.

The oxygen consumption of the placenta (and myometrium) is equal to the total oxygen delivered to the placenta and uterus less the total oxygen taken away from the placenta and uterus. Oxygen flow is equal to oxygen content multiplied by the blood flow. In any vessel, oxygen content is equal to ($Hb \times SO_2 \times 1.34$). The calculations to determine oxygen balance in the placenta require values for 12 parameters that are listed in Table 4.

Oxygen supply to the placenta (from mother and fetus) must be equal to the oxygen flow away from the placenta plus the oxygen consumption of the placenta and myometrium. Also, the results of our calculations can be checked to see if they agree with our predictions for fetal oxygen consumption and placental oxygen consumption.

Using the Typical Values Above

Oxygen delivery to the placenta (and uterus):

= Oxygen delivery in uterine artery + Oxygen delivery in umbilical artery

= $[(120 \times 1.34 \times 0.98) + (0.03 \times 100)] \times 0.6 + [(170 \times 1.34 \times 0.45) + (0.03 \times 18)] \times 0.3$

= (96.4 + 30.9) mLs O_2/min

= 127.3 mLs O_2/min

Table 4: pO_2, pCO_2 values in uterine and umbilical arteries.

Uterine artery	pO_2–100 mm Hg	pCO_2–32 mm Hg
Uterine vein	pO_2–75 mm Hg	pCO_2–45 mm Hg
Umbilical artery	pO_2–18 mm Hg	pCO_2–55 mm Hg
Umbilical vein	pO_2–28 mm Hg	pCO_2–40 mm Hg

by mansdocs.com

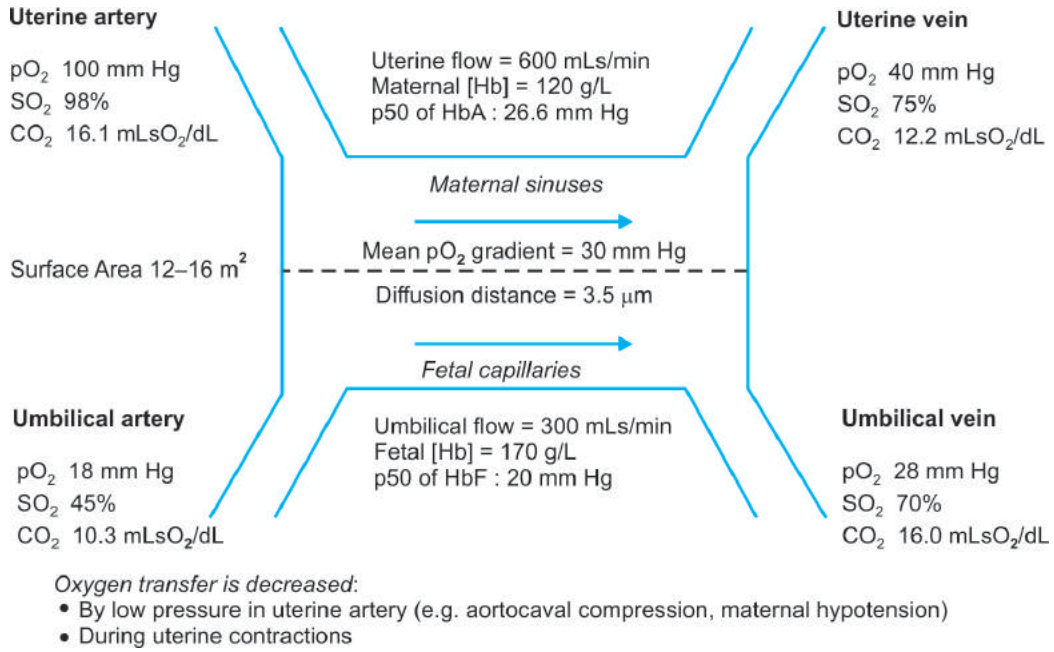


Fig. 3: Fetal oxygenation.

Fetal oxygen consumption:
= Oxygen flow in umbilical vein – oxygen flow in umbilical artery
= 48.1 – 30.9
= 17.2 mLs/min
Placental and myometrial oxygen consumption:
= Oxygen delivery to placenta – Oxygen carried away from placenta
= 127.3 – 121.2
= 6.1 mLs/min
Note that the combination of a low maternal Hb and the high fetal Hb requires either that the uterine artery flow is significantly higher than umbilical artery flow or that the oxygen extraction ratio in the placenta is high (or some combination of these two circumstances). Figure 3 shows the placental oxygen balance.

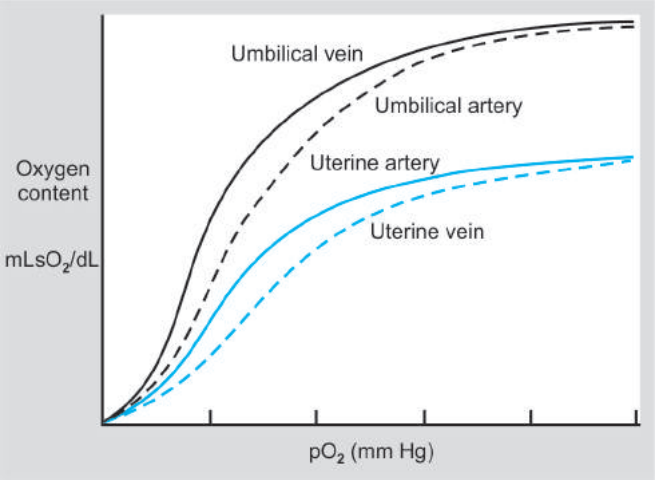


Fig. 4: Oxygen dissociation curves in fetal circulation.

Oxygen Dissociation Curves for Maternal and Fetal Hemoglobin (Fig. 4)

This involves drawing four dissociation curves because the curves for maternal HbA and fetal HbF are different and each requires a second curve to demonstrate the change in affinity due to the Bohr effect (i.e. the "double Bohr effect").

The use of oxygen content on the y-axis allows clear demonstration of the differences in content due to low Hb of the mother and high Hb of the fetus.

The position of the maternal ornithine decarboxylase (ODC) tends to be similar to that normal adult HbA. The low maternal pCO_2 tends to shift the curve to the left but the effect of this is minimized because two maternal arterial pH usually return to the normal range. An increased maternal red cell 2, 3 DPG also shifts the curve rightward.

Both maternal (HbA) and fetal (HbF) oxygen dissociation curves undergo a change in position due to the Bohr Effect. This is known as the "double Bohr effect" and is one of the factors that facilitates oxygen transfer from maternal blood to fetal blood.

by mansdocs.com

Can Permissive Hypercapnea be Allowed in Parturients with ARDS?

As you can see from above, a CO_2 gradient of minimum 10 mm Hg is needed for effective transfer between maternal and fetal circulation. Any decrease in gradient, as in permissive hypercapnea, results in fetal acidosis that may be detrimental. There have been no animal or human studies done to establish an allowable safe limit of permissive hypercapnea as part of lung protective ventilator strategy in ARDS in pregnancy, but current studies puts this limit of maternal PCO_2 as 55 mm Hg.

RADIOLOGIC PROCEDURES AND FETAL RISK

Despite the potential risk of exposing the fetus to ionizing radiation, radiological investigations may be required for optimal management of the pregnant critically ill patient. Fetal well-being depends on maternal recovery, and the mistake should not be made of avoiding necessary radiological procedures. Although radiation exposure in pregnancy carries definite risks, the likelihood of any adverse effect is about 0.1% per rad. Exposure to the fetus of less than 5 rads is therefore associated with a risk far below the spontaneous rate of congenital malformations. Nonetheless, it is likely that the risk to the fetus increases with increasing radiation dose, and therefore every effort should be made to minimize fetal exposure, particularly in the first trimester.

DRUG THERAPY

Pharmacotherapy during pregnancy requires consideration of the pharmacologic and teratogenic effects of drugs on the embryo or fetus. The major risk period for teratogenesis is the first 10 weeks of gestation. ACE-inhibitor, tetracycline, coumadin derivative and salicylates are strictly contraindicated and have potential to cause teratogenicity.

by mansdocs.com

CHAPTER

42

Respiratory Disorders During Pregnancy

Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

INTRODUCTION

Respiratory disorders are not uncommon during pregnancy. The respiratory adaptations associated with pregnancy sometimes confound the diagnosis of respiratory compromise in the pregnant state. The materno-placental unit needs higher PaO_2 and flow than is anticipated in nonpregnant women. The physiological changes during pregnancy make the initiation and maintenance of ventilator support difficult during pregnancy. Factors relevant to the intensivist while managing pregnant women presenting with asthma, acute respiratory distress syndrome (ARDS) and primary pulmonary hypertension will be discussed in this chapter.

ASTHMA

Asthma is one of the most common chronic conditions associated with pregnancy. It is a chronic inflammatory disease of the airways with episodic exacerbations characterized by hyper responsiveness to various stimuli. The prevalence of asthma during pregnancy is between 1% and 4%.

Effect on Pregnancy

Mild asthmatics usually progress to uneventful deliveries. Severe disease however has significant effect on maternal and fetal outcomes. Exacerbations are more likely to occur between 24 weeks and 36 weeks of pregnancy. Physiological changes of pregnancy which effect pathophysiology of asthma are listed in Box 1.

The adverse perinatal outcomes associated with severe asthma are listed in Box 2.

Pregnancy per se produces respiratory alkalosis. The partial pressures of O_2 and CO_2 are variable at various stages of pregnancy. The differential diagnosis of a breathless pregnant lady can vary from anemia to pulmonary embolism. It is essential to diagnose the reason for breathlessness for optimum care.

Box 1: Physiological changes affecting asthma in pregnancy.

- Increase in free cortisol levels might protect against inflammatory triggers
- Progesterone might improve airway responsiveness
- Increased prostaglandin F_2 α might worsen bronchoconstriction
- Placental 11β-hydroxysteroid dehydrogenase type 2 decreased activity might increase placental cortisol level and lower birth weight
- Placental gene expression of inflammatory cytokines may promote low birth weight
- Cell mediated immunity may be modified which alters maternal response to infection and inflammation

Box 2: Adverse perinatal outcomes associated with severe asthma.

- Pre-eclampsia
- Uterine hemorrhage
- Preterm labor
- Congenital anomalies
- Fetal growth restriction
- Low birth weight
- Neonatal hypoglycemia
- Complications of mechanical ventilation

by mansdocs.com

Asthma is usually episodic and is characterized by dry cough and wheezing, with triggers usually identified. Pulmonary function tests help in the diagnosis.

Pulmonary embolism usually has a much shorter temporal course and presents with dyspnea, pleuritic pain and sometimes hemoptysis. Deep venous thrombosis (DVT) is identifiable in close to 40% of patients. In pregnancy, perfusion scan might be considered as an alternative to computed tomography-pulmonary angiogram (CTPA) which gives more detailed diagnostic and prognostic information.

Pulmonary edema presents as acute or progressive respiratory distress associated with hypertension, tocolytic therapy or heart disease. Chest radiography coupled with echocardiography usually diagnostic.

Peripartum cardiomyopathy usually presents during the last month of pregnancy and the period of risk extends to 6 months postpartum. Features are suggestive of global myocardial dysfunction and diagnosed on echocardiography.

Amniotic fluid embolism presents as acute respiratory distress beginning around the time of uterine evacuation, resulting in disseminated intravascular coagulation (DIC) and cardiac arrest in extreme cases.

Management

The general principles of management of asthma apply to the pregnant lady with asthma as well. Overcautious withholding of essential anti asthma medications could jeopardize the fetal oxygenation and make the maternal asthma refractory to treatment. Early aggressive therapy is therefore recommended. The treatment has to be provided at optimal level through out pregnancy. A more frequent assessment of response to therapy is indicated. Comorbidities like rhinitis and gastric reflux should be aggressively addressed. This will usually be a good time to convince a smoker to give up the habit. A monthly pulmonary function test is indicated in these patients. The risk of pre-eclampsia and growth retardation should be remembered and reiterated to the patient. It is better to avoid the flu vaccine during the first 12 weeks of pregnancy. The partial pressure of oxygen should be maintained high enough to generate an SpO_2 of more than 95% till delivery is accomplizhed. At the same time the $PaCO_2$ should be allowed to exceed 40 mm Hg. Hospitalised patients should be nursed in the left lateral position. Crystalloids may be used in relevant quantities to maintain hemodynamics and hydration. Adrenaline may be used only in the case of anaphylactic reaction. Intubation of these women can be unpredictable and earlier intubation is safer.

All medications can be prescribed at full dose. Short acting β2 agonists or steroids should be given. Sometimes both agents may be necessary. Oral steroids have been reported to be associated with increased incidence of pre-eclampsia. Lumbar epidural analgesia is reportedly beneficial in reducing oxygen consumption. Patients who present with obtunded sensorium, silent chest, hypercarbia and peak expiratory flow rate (PEFR)/forced expiratory volume in 1 second (FEV1) less than 25% of predicted should be admitted in intensive care unit (ICU). Magnesium sulfhate is indicated in severe cases in the initial management.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome is a clinical syndrome characterized by hypoxemic respiratory failure resulting from alveolar hyper permeability as a consequence of pulmonary inflammation. Absence of a cardiac etiology is crucial to make a diagnosis of ARDS. It is however important to remember that ARDS is a manifestation and not a disease. It is rather a syndrome that can result from numerous causes. These causes are enumerated in Table 1. Identifying and treating the underlying condition is crucial for successful management of ARDS. The management of ARDS nevertheless involves certain core principles which remain constant irrespective of etiology. This chapter focuses on these on core principles.

Pathophysiologically, ARDS progresses through distinct phases. The first week is usually the exudative phase during which high protein pulmonary oedema floods the alveoli and produces surfactant abnormalities. This phase usually lasts for 4–7 days following which the pathophysiology either resolves or progresses to the fibroproliferative phase if the underlying disease is not appropriately treated. Clinically, the first week is characterized by hypoxemic respiratory failure and dyspnea with bilateral crackles and infiltrates on chest X-ray (CXR).

By virtue of its effect on maternal oxygenation, ARDS can cause fetal death, preterm labor and perinatal asphyxia amongst survivors. It is important to manage the oxygenation while ensuring maternal safety. The targets have to be modified from general population to maintain an SpO_2 more than 90% and PaO_2 more than 80 mm Hg. The management of ARDS can be divided into nonventilatory and ventilatory strategies. While mechanical ventilation

by mansdocs.com

Table 1: Etiological causes of acute respiratory distress syndrome (ARDS).

Unaffected by pregnancy	*Modified by pregnancy*	*Unique to pregnancy*
Direct/Pulmonary		
• Pneumonia	• Gastric aspiration	• Tocolytic associated pulmonary edema
• Inhalational injury	• Viral pneumonia	• Amniotic fluid embolism
• Chemical pneumonitis	• Air embolism	
• Near drowning	• Coccidioidomycosis	
• Pulmonary contusion		
• Fat embolism		
Indirect/extrapilmonary		• Pre-eclampsia
• Sepsis	• Pyelonephritis	• Eclampsia
• Trauma	• Malaria	• HELLP
• Burns		• AFLP
• Pancreatitis		• Chorioamnionitis
• TRALI		

(TRALI: Transfusion related acute lung injury; AFLP: Acute fatty liver of pregnancy'; HELLP: Hemolysis, elevated liver enzymes, low platelet count).

is the mainstay of management of hypoxemic respiratory failure, nonventilatory strategies contribute significantly to the successful management of this potentially lethal condition.

Nonventilatory Strategies

Fluid Balance

One of the most crucial determinants of safe management of ARDS is proper management of fluid balance. It is not uncommon for patients with ARDS to present with hemodynamic instability secondary to the underlying disease. Fluid resuscitation is usually the first response. However, persistent positive fluid balance after the first 24 hours of resuscitation is recognized as a determinant of longer ICU and hospital stay. Moderation in fluid administration after the initial phase of resuscitation is recommended for the management of ARDS. At the same time, diuretic use has not been shown to be associated with better outcomes. Initiation of ultrafiltration by extra corporeal techniques is probably preferable.

Steroids

Understanding of the pathophysiology of ARDS, would seem to indicate a role for steroids in the management of the condition. However, literature review does not support a positive effect of steroids on the outcome of patients with ARDS. What is definitely known is the fact that initiation of steroids in the second week of illness is associated with a higher incidence of secondary infections and critical illness polyneuropathy. Use of steroids in the first week of illness is a graey zone with no evidence either for or against the use. A subset of patients whose ARDS is a consequence of pneumonia tend to have higher P/f ratios when hydrocortisone is administered as an infusion at a rate not exceeding 300 mg/day.

Sedation and Paralysis

The mechanical ventilation strategies used in the management of ARDS, usually warrant the use of deeper sedation and quite often the use of neuromuscular blockers. A balance has to be struck between adequate sedation for safe ventilation and over sedation with prolonged ICU stay. A daily sedation interruption was considered essential for the daily assessment of such patients. However, more recent data seems to suggest no effect of such a strategy. Continuous infusions of benzodiazepines are no longer recommended.

Opioid infusions, usually with fentanyl, are preferred agents for appropriate sedation during the acute phase of management. The newer sedative agent dexmedetomidine provides deeper sedation but has no effect on respiratory trigger. Although this aspect is beneficial in mild disease, it might not help the cause in patients with severe ARDS in whom controlled ventilation is desirable. Neuromuscular blockade which is viewed with lot of concern might have to be used in the first 24–48 hours of ventilation for ARDS.

Blood Transfusions

The hazards of blood transfusion in critically ill patients are now well recognised. It is now very clear that blood

by mansdocs.com

transfusions should not be used as a strategy to correct hypoxemia. A hematocrit of 21% is sufficient for oxygen delivery during critical illness.

Nutrition

ARDS is a high stress state and nutritional parameters need to be optimized to prevent accumulation of fluid in third spaces. Appropriate charting of components of nutrition needs to be made to minimize CO_2 production. ω 3 fatty acids were initially believed to be beneficial in all ARDS patients but recent evidence has not shown impressive results.

Ventilatory Strategies

Mechanical ventilation is expected to be a routine intervention for the management of ARDS. However, the intrinsic nature of the disease characterized by low compliance and tendency for air leaks, makes mechanical ventilation hazardous in these patients. Certain practice guidelines have been suggested by the NIH-ARDS net group which seeks to minimize the dangers of mechanical ventilation in ARDS.

Tidal Volume

The ARDS net guidelines suggest that the delivered tidal volume should not exceed 8 mL/kg of ideal bodyweight (IBW). Several formulae are available to predict the IBW, but the simplest one seems to be length (in cms) – 100. The least tidal volume that can be set is around 4 mL/kg IBW. This might result in a build up of CO_2 but can be accepted as long as the pH remains more than 7.2.

Plateau Pressures

The recommended plateau pressure limit in patients with ARDS is 35 cm H_2O. The tidal volumes have to be adjusted to keep the pressures less than this threshold.

Positive End-Expiratory Pressure

This is probably the most misunderstood and therefore dreaded setting during mechanical ventilation for ARDS. Positive end-expiratory pressure (PEEP) probably is the mainstay for achieving proper oxygenation in ARDS. When applied judiciously and correctly it helps to achieve the targets of oxygenation quite efficiently. A PEEP setting of 12–14 cm H_2O is probably optimal. Higher settings do show some anecdotal benefit, but evidence does not seem to support the use of PEEP settings higher than 14. Below this level, its effects on hemodynamics are also minimal.

Inverse Ratio Ventilation

The rationale of increasing the inspiratory phase and sometimes exceeding the expiratory phase comes from the beneficial effects of PEEP. This maneuver is often used with pressure controlled ventilation with acceptable success.

Prone Ventilation

This is the most physiological intervention for the management of ARDS. Ventilating a patient prone works by several mechanisms, including improving air flow to the better perfused area in the lung, taking the weight of the heart and great vessels off the lungs and easier clearance of secretions. This is however, a labur intensive intervention and needs meticulous team work for successful execution.

High Frequency Ventilation

This mode of ventilating the lungs with very high frequencies permits the generation and retention of PEEP thus keeping the diseased alveoli open. The initial enthusiasm for using this mode has been dampened by the publication of two recent randomized controlled trials (RCTs) which showed probable harm with this mode.

Extra corporeal membrane oxygenation is a non-ventilatory extra corporeal technique which is being increasingly being recommended for severe ARDS, not responding to conventional treatment. It involves circulating the blood through an oxygenator and returning it to the circulation while allowing the native lung to recover. It has an added advantage of supporting a poorly functioning heart which worsens the situation of ARDS.

Pulmonary Hypertension

Pulmonary hypertension complicating pregnancy is one condition which has a uniformly high perinatal mortality rate (as high as 56%). Pregnancies in patients with pre-existent pulmonary hypertension are less likely to reach viability as a consequence of the inability of the hemodynamic system to sustain the physiological stress of later stages of pregnancy. Pulmonary hypertension acquired during pregnancy also challenges the maternal system significantly.

by mansdocs.com

Several conditions can produce pulmonary hypertension during pregnancy. ARDS is probably the most common. Thrombo embolic disease, hypercoagulable states, amniotic fluid embolism and congenital heart disease are other more common etiological factors. The final common pathway is right ventricular strain and failure.

Clinical presentation is with cough, shortness of breath and chest pain. Right ventricular failure may present as dizziness and syncope. A loud pulmonary component of second heart sound is often heard in association with a raised JVP. A systolic murmur of tricuspid regurgitation aggravated by inspiration is classical. Chronic PAH is associated with raised BNP which has prognostic value in patients with pulmonary thrombo embolism. CXR is often useful to identify pulmonary parenchymal causes of PAH. CT Pulmonary angiography identifies thromboembolic disease. Trans thoracic echo is useful to identify the right heart gradients.

Meticulous attention to fluid balance is crucial while making a conscious effort to avoid hypovolemia. Right ventricular function may be augmented by dobutamine which however can cause hypotension by increasing pulmonary vascular resistance in doses exceeding 10 μg/kg/min. The phosphodiesterase inhibitor, milrinone, has a better profile than dobutamine, with better action shown with aerosolized delivery. The calcium channel senstizer, levosemendan, is a promising agent which needs further studies. Vasopressors like norepinephrine and phenylephrine may be needed to maintain the systemic pressures above the pulmonary pressures. However, all vasopressors have effects on pulmonary vasculature and need to be titrated carefully. Vasopressin in lower doses has beneficial effects but needs further study. Agents with predominant β-stimulating properties tend to decrease uterine blood flow. Pulmonary vasodilators like prostacyclins and calcium channel blockers can be used in selected patients. Sildenafil causes pulmonary and systemic vasodilatation and has a positive inotropic action on the hypertrophic right ventricle. It is category B drug in pregnancy and experience is limited.

by mansdocs.com

CHAPTER

43

Liver Disease Complicating Pregnancy

Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

INTRODUCTION

Liver disease complicating pregnancy is a challenge to the health care professionals managing these patients. The physiological changes in pregnancy will have an impact on the diagnosis of liver disorders just as with other medical conditions associated with pregnancy. The effects of a dysfunctional liver on the materno-fetal homeostasis can be catastrophic. Prompt and correct recognition of the disorder is essential. Physiological changes of pregnancy of relevance to liver function are summarised in Table 1.

Liver diseases during pregnancy can multiple causes. Some of the disorders are unique to pregnancy like HELLP syndrome and Acute Fatty Liver of Pregnancy. Some of the disorders are coincidental to pregnancy but have a more severe course or are predisposed by the hypercoagulable state of pregnancy. Examples include viral hepatitis and Budd Chiari syndrome. Some other disorders are purely coincidental with the course and outcome unchanged when compared to the nonpregnant population. A complete list is provided in Table 2.

Cirrhosis and Portal Hypertension is a relatively rare phenomenon during pregnancy, with a prevalence of

Table 1: Impact of physiological changes of pregnancy on liver function.

Parameters that are increased
• Blood volume and cardiac output
• Alkaline phosphatase – rise 3–4 fold
• Clotting factors I, II, V, VII, VIII, X and XII
• Ceruloplasmin levels
• Transferrin levels
Parameters that are decreased
• Gall bladder contractility
• Uric acid levels
• Total protein and albumin levels
• Anti-thrombin III and protein S level
Parameters that remain unchanged
• Transaminase levels
• GGT and bilirubin levels
• PT and platelets

Table 2: Liver diseases in pregnancy.

Unrelated to pregnancy	*Coincidental to pregnancy*	*Peculiar to pregnancy*
• Cirrhosis and portal	• Budd-Chiari syndrome	• HELLP
• Hypertension	• Viral Hepatitis A to E	• AFLP
• Auto immune hepatitis	• Alcohol related disease	• Intra hepatic cholestasis in pregnancy
• Primary sclerosing cholangitis	• Gallstone disease	• Hyperemesis gravidarum
• Storage disorders	• Tropical diseases	
• Chronic viral hepatitis		

by mansdocs.com

Table 3: Features of acute viral hepatitis in pregnancy.

Virus	*Risk of fetal transmission*	*Signs and Symptoms*	*Treatment*	*Outcome*
HEV	In Utero 50%	Jaundice, Hepatic failure	Prevention	Mortality up to 40%
HSV	In utero and during delivery up to 50%	Elevation in bilirubin, enzymes and INR	Acyclovir	Liver failure mortality up to 40%
HAV	Rare	May be asymptomatic	Supportive	Benign
HBV	High if mother is HBe A g^+ and during third trimester	Viral syndrome or could be aymptomatic	Supportive	Benign
HCV	3.8%	Often asymptomatic	Supportive	Benign
CMV	Up to 30–40%	Mononucleosis like	Supportive	High morbidity to child

about 0.45 per 1000 pregnancies. The increased demands of advancing pregnancy will subject the borderline liver to higher metabolic stress. Women with long term cirrhotic livers are quite often infertile. However, before planning assisted reproduction, the primary liver disease should be treated or well supported prior to conception and continued during pregnancy. Premature deliveries are also more common in this population. Diuretics and Spironolactone which are routinely prescribed during hepatic decompensation, are contra indicated during pregnancy. Bleeding varices can be safely banded or sclerosed during pregnancy.

Auto Immune Hepatitis: Pregnancy induces a state of immune tolerance in an effort to support the "foreign" fetus. This phenomenon confers a state of improvement of the underlying auto immune hepatitis, facilitating a lowering in the dose of immunomodulating agents already in use. However, one in four patients will have a flare of the disease in the immediate postpartum period. Prematurity, low birth weight and perinatal fetal loss are associated with this disease. Immunosuppressive therapy is not contraindicated. Prednisolone and Azathioprine are known to be safe during pregnancy and lactation.

Primary Sclerosing Cholangitis: This is also an auto immune disorder which can overlap with auto immune hepatitis, with conception and successful outcomes relatively rare. The pruritus associated with the disease can worsen during pregnancy. Ursodeoxycholate can be safely used in Primary biliary cirrhosis. Sclerosing cholangitis is much less likely to be associated with pregnancy continuation and treatment options are also limited.

Budd Chiari Syndrome: This is a hepatic veno occlusive disease that is characterized by hepato cellular necrosis around the central vein. Mechanical factors and the hypercoagulability of pregnancy seem to be associated with the disease. It manifests more often in the postpartum period. Underlying hypercoagulable states like protein C and S deficiency and Anti-thrombin III deficiency and factor V Leiden mutations are seen in around 25% of patients. Budd Chiari Syndrome could be a manifestation of the Anti-Phospholipid Antibody Syndrome. The disease is characterized by abdominal pain, hepatomegaly and ascites. Hepato-Jugular Reflux is often not seen. Doppler assessment with MR angiography confirms the diagnosis. Full anti-coagulation throughout pregnancy and puerperium is recommended.

Viral Hepatitis: Viral hepatitis has an incidence of 1–2 per 1000 pregnancies. The outcomes of Hepatitis E and Herpes Simplex Hepatitis are significantly poorer than in the non pregnant population. The salient features of infections with different hepatotropic viruses are summarized in Table 3.

Acute Fatty Liver of Pregnancy: The disorder usually manifests in third trimester with an incidence of 0.01% of pregnancies. Elderly primiparous women, women carrying twin gestations (male) are at higher risk. Presentation is with nausea vomiting and abdominal pain. Delayed diagnosis could lead to DIC and hepatic failure. The basic abnormality is a defect in fatty acid oxidation resulting in fatty acid deposition in the liver. Liver biopsy may be required for diagnosis. Delivery usually resolves the pathophysiology. The neonates homozygous for the LCHAD enzyme born to heterozygous mothers can have a stormy course. AFLP can recur in subsequent pregnancies.

HELLP Syndrome: It is usually a complication of pre-eclampsia and eclampsia. It can also occur independent of the two disorders. One-third of patients develop the syndrome in the postpartum period. Advanced maternal age and multi parity are risk factors. The basic abnormality seems to be a micro angiopathic hemolytic anemia and

by mansdocs.com

Table 4: Summary of hepatic disorders peculiar to pregnancy.

Disorder	*Gestational period*	*Prevalence*	*Symptoms*	*Lab tests*	*Outcome*	*Treatment*
Hyperemesis Gravidarum	First trimester. Resolves around 20 weeks	< 2% Primi	Nausea Vomiting	AST/ALT > 1000U ALT>AST Low TSH	Benign	IV Fluids Thiamine Pyridoxine Promethazine
Intrahepatic Cholestasis	Second trimester	< 20% Multiple gestations	Pruritus Resolves postpartum	AST/ALT > 1000 GGT normal PT normal Bil < 6 mg	Increased gallstones Recurrent Fetal distress	Ursodeoxycholate Delivery for fetal distress
AFLP	Third trimester	1:13000 Primi Multiple gestations	FHF DI	Platelets <100000 AST/ALT>300 PT high Fibrinogen low DIC	Maternal mortality <20% Fetal Mortality > 40% Test for LCHAD	Prompt delivery Transplant
Eclampsia/ Pre-eclampsia	Beyond 20 weeks Recurrent	5% Multiparous Multiple gestations	Proteinuria HTN Renal Failure Seizures Pulmonary edema	Elevated Uric Acid levels	Maternal Mortality 1% Prematurity and fetal death 5–30%	HTN control MgSO4 Delivery
HELLP	Beyond 22 weeks and postpartum	0.5%	Abdominal pain, seizures, AKI, Pulm edema Hepatic rupture	Platelets < 100000 Hemolysis High LDH AST/ALT up to 6000 DIC	Maternal mortality 60% with hepatic rupture Fetal death 1–30%	Prompt delivery

platelet consumption. Fibrin deposition in hepatic sinusoids can cause transaminase elevation and progress to hepatic necrosis. Capsular tears and sub capsular hematomas can also occur. Right upper quadrant pain associated with nausea, vomiting and jaundice is the classical presentation. Headache (30–60%) and visual symptoms (17%) can also occur. Hypertension is a feature in up to 80% of patients. Hemolysis, elevated transaminases and low platelets define the syndrome. Hemolysis is better diagnosed by demonstration of schistocytes on peripheral smear. Thrombocytopenia severity is used to categorize the syndrome and disease severity is highest amongst those with all three abnormalities. Control of hypertension is crucial. Delivery is therapeutic for the condition. For pregnancies younger than 34 weeks, a course of betamethasone 12 mg daily for 2 days followed by delivery on third day might be beneficial. This strategy has not been supported by more recent evidence. Platelet transfusions should be reserved for patients scheduled for cesarean section with counts less than 50000/ cumm. Overt bleeding might warrant transfusions at higher counts. Risk of maternal death is around 1%. Complications include AKI, DIC, ARDS, Stroke and Hepatic rupture. It is a risk factor for Pre-Eclampsia and Eclampsia in subsequent pregnancies.

Hepatic disorders peculiar to pregnancy are summarized in Table 4.

Tropical diseases like malaria, leptospirosis, scrub typhus and dengue hemorrhagic fever should also figure in the differential diagnosis for a jaundiced pregnant woman.

by mansdocs.com

CHAPTER

44

Peripartum and Postpartum Intensive Care in Pregnancy

Rajesh Chandra Mishra, Pratibha Dileep, Srinivas Samvedam, Sunil P Pandya

INTRODUCTION

Care of sick pregnant mothers in dedicated obstetric intensive care units (ICUs) has immensely changed the facet of maternal and neonatal outcomes. Improved anesthesia care in this subset of population has also added a major component of maternal satisfaction and maternal-fetal safety and early maternal bonding, despite the fact that ~80% of sick mothers either deliver prematurely and babies are born with low cord pH due to underlying medical problems.

Regional anesthesia in thus sick parturients if judiciously decided is of great benefit. General endotracheal anesthesia (GETA) has its central role when the patient is hemodynamically unstable and had multiple organ dysfunction syndrome (MODS) with coagulopathy. Airway in obstetrics is difficult, incidence being 1:280. The incidence of difficult airway in obstetric ICU is 1:10. This is another reason why regional anesthesia is among the preferred anesthesia technique in obstetric ICU.

Central neuraxial techniques have remained the gold standard for pain relief during labor and operative surgeries. It has an excellent safety record; however, occasionally the epidurals and spinals can misbehave and be a double-edged sword especially in a setting of obstetric ICU. Non-neuraxial regional anesthesia techniques like peripheral limb blocks or blocks for acute pain management are usually confined to trauma pregnant patients. By and large central neuraxial blocks (CNBs) are the commonest regional anesthesia techniques employed for labor and operative deliveries for parturients requiring intensive care.

The development of subspecialties in obstetrics, anesthesia and pediatrics has resulted in improved maternal and perinatal care in maternal ICUs and neonatal ICUs. Decision to deliver of often multidisciplinary. The most common reasons for maternal ICU admission are hypertensive disorders, massive obstetric hemorrhage and sepsis. Parturients with chronic kidney and liver diseases, corrected/residual defects/uncorrected congenital heart disease patients, hemoglobinopathies, thrombophilias, systemic lupus erythematosus (SLE) and several other comorbid medical disorders. Mothers who could never dream of becoming pregnant are conceiving and are referred to high-risk centers.

Creation of ICU at delivery site (labor suite) or changing the ICU bed into a delivery bed in critical care unit is of paramount importance for safe confinement of these women during peripartum period. Certain occasions, when the mother is on stiff organ supports, even the cesarean section may have to be carried out in ICU.

Providing safe regional analgesia for labor and anesthesia for operative deliveries or other procedures (quite often in an emergency setting) to these parturients without compromising maternal physiology and fetal well-being is indeed challenging and demands multidisciplinary liaison and planning, skills, knowledge, experience and evidence-based anesthetic practice.

The anesthesiologist has to be well versed with the resuscitation protocols/ICU policies that stabilize and restore near normal maternal and fetal physiology in all these conditions so as establish regional anesthesia safely.

by mansdocs.com

PERIPARTUM ISSUES AND ANESTHETIC CONSIDERATIONS

Maternal Sepsis

- Catheter-based central neuraxial techniques [epidural, combined spinal-epidural anesthesia (CSEA) and continuous spinal] and spinal anesthesia in parturients in hemodynamically unstable patients with fulminant sepsis are unsafe as sympatholysis induced by CNBs can worsen hemodynamics. Further, catheter-based techniques and spinals have a potential to cause neuraxial infections, e.g. meningitis, epidural abscess, etc.
- Stable patients with bacteremia and under antibiotic cover, regional anesthesia is not a contraindication. Similarly, patients with severe maternal sepsis adequately treated and stabilized, regional anesthesia can be given.
- Maternal sepsis is likely to be associated with low platelets and disseminated intravascular coagulation (DIC) and risk versus benefit of regional anesthesia has to be weighed appropriately. Do not compromise on multiorgan supportive and protective strategies.
- Ensure that epidural bacterial filter is in place, patient is receiving appropriate antibiotic cover and catheter to be removed at the earliest if pyrexia continues, to minimize epidural tip colonization.
- Suspected neuraxial infections with indwelling epidural catheter, flush the catheter with saline, aspirate, remove the catheter and send the tip for culture and sensitivity. Look for any local infection or discharge; send it for culture and sensitivity.
- Neurology consult/intervention and magnetic resonance imaging (MRI) with gadolinium contrast should be done as soon as possible in appropriate cases.

Anticoagulants, Coagulopathy and CNBs

- More than 80% of maternal ICU admission patients have underlying coagulopathy.
- *The three commonest indications of maternal ICU admissions namely:* (1) hypertensive disorders, (2) hemorrhage and (3) sepsis can be associated with coagulopathy. Further, several other medical comorbid disorders, e.g. thromboembolism, antiphospholipid antibody (APLA) syndrome, prosthetic heart valves, obesity, etc. warrant either thrombo-prophylaxis or full anticoagulation.
- Neuraxial hematoma is rare, but with undergoing coagulopathy and anticoagulation, they are not uncommon. There are several case reports of neuraxial hematoma in obstetrics, more commonly occur spontaneously, sometimes, following regional anesthesia techniques especially in conditions like hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, etc.
- CNBs in these subset of patients mandate practicing standard guidelines (ASRA, Feb. 2010; ESRA, 2011) both at insertion and removal of epidural catheters.
- Every unit that practices regional anesthesia should have a protocol for "the block that does not regress" and "safety net".
- Neuraxial hematoma, like epidural abscess, mandates appropriate radiological consult (MRI with contrast) and early neurological intervention, ideally within 12 hours!

Respiratory Failure and Cardiac Failure in Pregnancy

- Combined spinal-epidural anesthesia are the ideal techniques for parturients with respiratory or cardiac failure. Good pain relief either for labor or postoperative pain has several advantages. It not only optimizes oxygen delivery, but also improves diaphragmatic function, acid-base status both in the mother and the fetus, facilitates and helps in weaning from mechanical ventilation, promotes early ambulation and thus facilitates early enteral nutrition.
- Regional techniques are boon in parturients with respiratory failure or those who have cardiac diseases especially the New York Heart Association (NYHA) class III/IV. Graded and programmed epidurals provide stable hemodynamics. Techniques that cause rapid sympathetic blockade like spinals, conventional dose spinals, and single-shot epidurals should be avoided in patients with poor cardio-pulmonary reserve.
- Antenatal patients requiring ventilator support, also benefit from epidural if they are induced or set into labor. It optimizes ventilator requirements and minimizes sedation.
- It is mandatory that while providing acute pain services to these patients, standards of ICU care are not compromized.

CNS Disorders, Musculoskeletal Disorders and CNBs

- Central neuraxial blocks are unsafe in parturients intracranial space-occupying lesions (SOLs) with raised intracranial pressure (ICP).

by mansdocs.com

- Patients with scoliotic spines or skeletal deformities may benefit with CNBs performed under vision, i.e. USG-guided neuraxial blocks.
- Patients with progressive neurological conditions and muscular dystrophies need proper evaluation, counseling and documentation before embarking upon these techniques.
- Rapid bolus epidurals can suddenly lead to a rapid increase in ICP and can compromise cerebral perfusion pressure or cause tonic and clonic seizure. Inadvertent wet tap or spinal in extremes of cases can cause cerebral herniation and coning.
- Toxic neuropathies and demyelinating neuropathies are common in ICU settings and regional anesthesia in these settings mandates meticulous technique and evidence-based practice.
- Slow continuous infusions are better methods of providing pain relief in parturients with intracranial arteriovenous malformations (AVMs), SOLs (tumors/bleeds) as Valsalva maneuver can be avoided.

Pain Syndromes in Obstetric Intensive Care Unit

- Patients in ICU with painful syndromes like acute disk herniation, herpetic neuralgias (thoracic/inguinal distribution) and acute pancreatitis pain immensely benefit from catheter-congruent analgesia and epidural steroids along with other supportive measures.
- We have had a series of antenatal patients with acute pancreatitis pain requiring greater than 1,000 μg of fentanyl, benefiting from low-dose mixture administered via thoracic epidural.
- Pregnant trauma victims also benefit from peripheral limb blocks and intercostal nerve blocks in case of rib fractures. USG-guided procedures accurately localize the nerve and help in reducing the dosage of local anesthetics.
- Transversus abdominis plane (TAP) block for lower abdominal surgeries or multi- orifice catheter infusion techniques are also good alternate modalities of pain relief in these patients.

GENERAL ENDOTRACHEAL ANESTHESIA IN ICU PATIENTS

When regional anesthesia is inappropriate and contraindicated, providing safe GETA becomes mandatory. Acid aspiration prophylaxis is an important consideration.

Parturients with either a septic or hemorrhagic/cardiogenic shock with severe metabolic acidosis (pH < 7.15) need a special mention. Rapid sequence GETA is unsafe and can virtually lead to cardiac arrest. These mothers need rapid volume stabilization with crystalloids and vasopressors and inotropes if no improvement. If mother is conscious and relatively stable, better to insert an arterial line and central venous pressure (CVP) line in internal jugular vein (IJV). Subclavian route should preferably be avoided as underlying coagulopathy is usually present and inadvertent arterial puncture can be serious complication.

While these are carried out, preoxygenation with 100% oxygen with either Bain's circuit or with continuous positive airway pressure (CPAP) mask via ventilator improves the functional residual capacity (FRC). Modified rapid sequence technique is followed in parturients with pre-existing severe maternal hypoxemia. This involves gentle mask ventilation with cricoid pressure after giving short-acting depolarizing muscle relaxant like suxamethonium.

Anuric patients should be investigated with point- of-care arterial blood gas (ABG) and electrolytes to rule out hyperkalemia. Suxamethonium can cause fatal cardiac arrhythmias if potassium is greater than 6 mmol/L. If this facility for rapid reporting is unavailable then either avoid suxamethonium or use other short-acting muscle relaxant like rocuronium in suspected hyperkalemia patients (ECG is also a helpful bedside tool is assessing hyperkalemic changes). The preferred induction agents are fentanyl 1–2 μg/kg and ketamine 1 mg/kg body weight. Etomidate even though offers hemodynamic stability is less frequently used due to fears of adrenal suppression.

While mother is being stabilized, ensure that there is a wedge under the right hip and manual left uterine displacement is continuously provided as supine posture leads to severe reduction in preload and increase in afterload, which are undesirable and preventable by this simple maneuver.

WHEN TO DELIVER

Sick mothers or pregnant trauma victims requiring ICU admission often pose this challenge about timing of delivery, more so if the gestational age has attained fetal viability (22–24 weeks, western standards and 26–28 weeks arbitrary Indian standards).

Several factors have to be considered and serial assessments using ultrasound, Doppler's, fetal non-stress tests (NSTs), ST-segment analysis (STAN), scalp pH, etc.

by mansdocs.com

may be necessary. The goal of the team should be focused primarily on maternal well-being and later on fetal well-being, giving best to both lives should be the ultimate goal. To a large extent, this is possible only in dedicated obstetric ICUs as the experienced personnel from the concerned departments are often unavailable in general ICUs. Inputs from experienced maternal medicine specialist, fetal medicine specialist and anesthesia and critical care team are all mandatory for the timely delivery of the fetus.

The Flowcharts 1 and 2 depict algorithmic approach that is our institute has made and we follow.

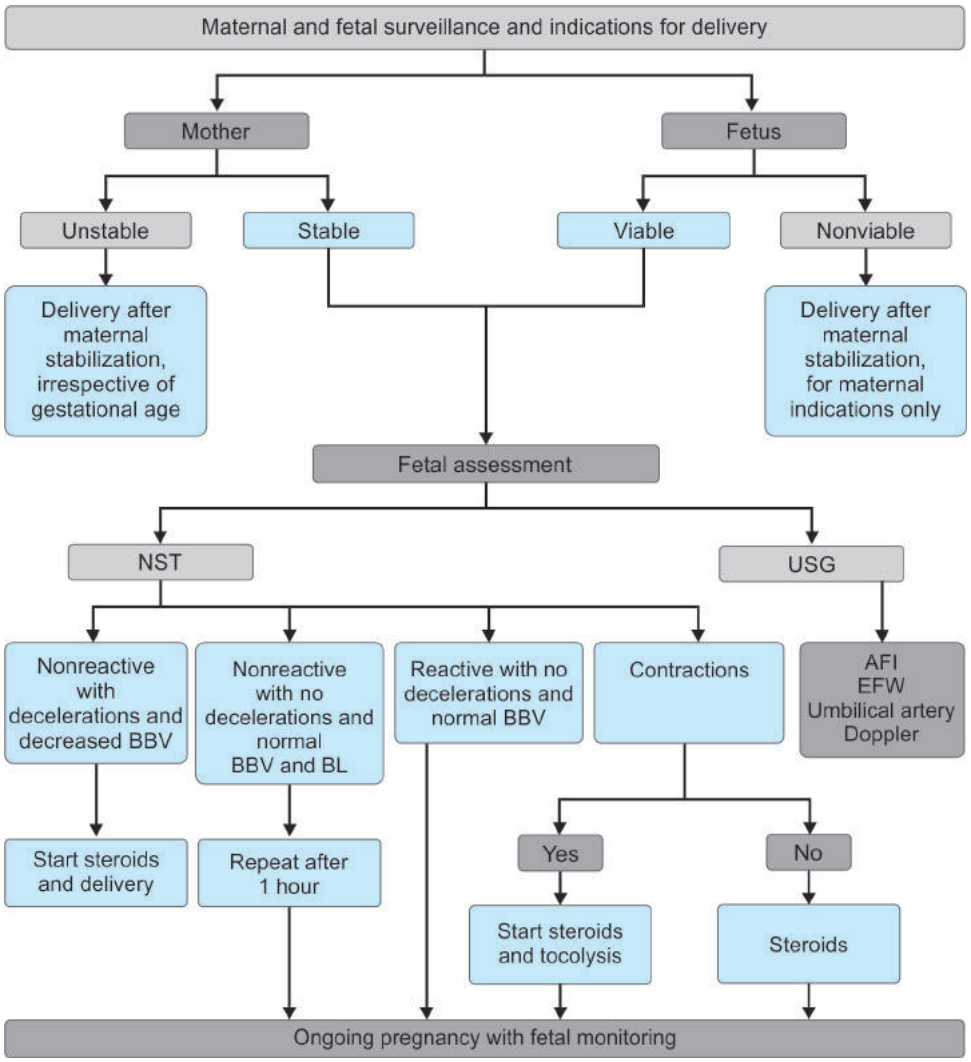
Other Ethical Considerations

Pregnant trauma victims with severe traumatic brain-injury on organ supports with good fetal well-being are an ethical dilemma, whether to continue organ supports to attain appropriate fetal viability at the end of which cesarean section is carried out. These decisions should be taken by the hospital ethics committee involving the family members in the decisions as there would be cost consideration in our country.

CONCLUSION

- Regional anesthesia is the technique of choice for providing pain relief in labor or for cesarean sections in parturients requiring ICU admissions.
- Regional anesthesia and analgesia in the critically ill can help to improve respiratory function, bowel function, mental status and patient comfort secondary to its opioid-sparing effects.

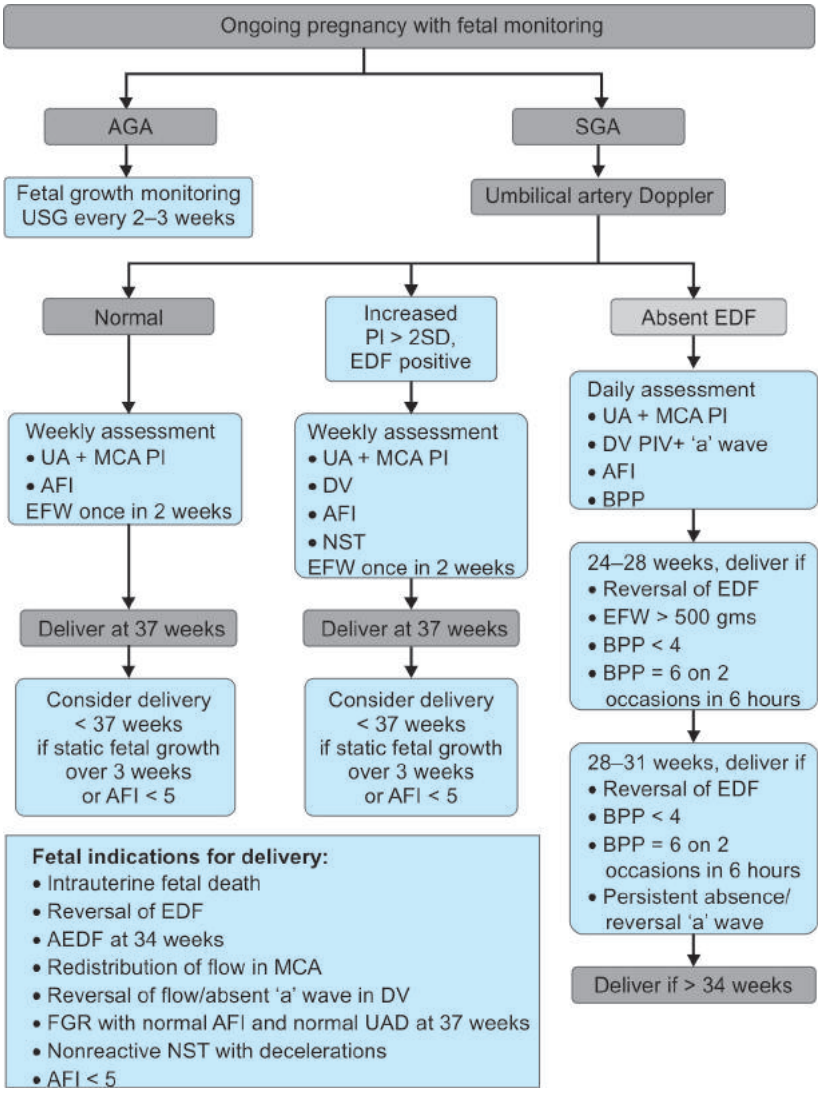
Flowchart 1: Algorithmic approach to pregnancy and delivery.



(NST: Non-stress test; AFI: Amniotic fluid index; EFW: Estimated fetal weight; USG: Ultrasound; BBV: Beat-to-beat variability).

by mansdocs.com

Flowchart 2: Algorithmic approach to fetal monitoring in pregnancy.



(AGA: Appropriate for gestational age; SGA: Small for gestational age; EDF: End-diastolic flow; ESW: Estimated fetal weight; MCA PI: Middle cerebral artery pulsatility index; AFI: Amniotic fluid index; DV: Ductus venosus; UA: Umbilical artery; BPP: Biophysical profile; EFW: Estimated Fetal weight; AEDF: Absent end-diastolic flow; FGR: Fetal growth restriction; UAD: Uterine artery doppler; NST: Non-stress test).

- Limitations for the use of regional anesthetic techniques are mainly associated with bleeding risks, hemodynamic side effects, difficulties in neurologic assessment and the potential of local anesthetic toxicity. Every unit that practices regional anesthesia in an ICU setting should have a protocol for "safety net" and "the block that does not regress".
- Sepsis and hypovolemia are relative contraindication. Standard resuscitation protocols and appropriate antibiotic cover are mandatory.
- GETA should be the technique of choice in parturients with unstable hemodynamics, neurological problems and coagulopathy.
- Peripheral nerve blocks, intercostal nerve blocks, thoracic epidurals in appropriate settings are of immense benefit to a subset of patients with acute pain syndromes.
- Termination of pregnancy decisions and ethical considerations should always be multidisciplinary involving obstetrician, maternal and fetal medicine specialist, anesthesia and critical care team and neonatology team.

CARE OF BRAIN-DEAD MOTHER

Brain death is a pathophysiological condition with important connotations to the Intensivist in terms of Organ

by mansdocs.com

Support and Ethical Dilemmas. Although the condition was first described by Mollaret and Goulon more than 50 years ago, the developing world has been relatively slow in adopting the criteria for diagnosis and protocolizing the care of a potential donor. The awareness of the need for an aggressive approach to a brain dead patient has only recently increased, as a result of a more widespread of availability of facilities for solid organ transplantation. The etiology for brain death in our country is not very extensively reported in literature. It is expected that tropical diseases and toxidromes would contribute to a significant number of patients being diagnosed as brain death, unlike the western data which mentions trauma as the leading contributor.

The relevance of brain death to a general intensivist is likely to be different from the relevance to a practitioner of obstetric critical care. While the general intensivist would be keen to support the brain dead patient for purposes of organ harvest, the obstetric intensivist would have to factor the well-being of the fetus as a priority while dealing with a brain dead pregnant lady. All treatment strategies will be tailored to facilitate supporting the mother so that a viable and healthy child can be delivered. This objective should receive top priority while efforts are made to identify potential recipients. Organ donation issues might be considered after the delivery of the baby is complete. Ethically it would not be considered in appropriate to continue life supports till the twin objectives of child birth and organ harvest are accomplished.

The criteria for diagnosis of brain death are well established in clinical practice. A detailed description of the process of certification of brain death is beyond the scope of this chapter. Several online resources outline the principles reasonably well. A brief summary is presented here. Brain stem death is essential for a diagnosis of brain death. Factors confounding the diagnosis of brain dysfunction should be excluded before diagnosing brain death. Pupillary reaction is crucial but not the size and equality. Apnea testing is mandatory. The diagnosis of brain death is essentially clinical. Clinical examination should be repeated after a 6-hour waiting period. Although diagnosis of brain death can be done by a single physician, the process of certification has to be done by a team of medical professionals, based on institutional and national policies.

Fortunately, the situation of a brain dead mother needing organ support is not too frequent. Literature review suggests that fewer than 50 such situations have been evaluated and reported. Therefore, recommendations for management of this condition will have to follow general principles of "brain death" management and some anecdotal peculiarities of the pregnant state of the victim.

All over the world, trauma seems to be the main contributor for the cause of brain death in pregnant women. Majority of victims seem to be aged around 25–26 years. The average duration of support for such unfortunate victims is fairly long at 38 days. The mean duration of pregnancy is reported to be 22 weeks with the mean delivery date being 28 weeks. Delivery was necessitated by maternal hemodynamic instability and fetal distress in majority of the cases. All live deliveries were achieved by cesarean section. A viable child could be delivered in 63% of patients. Birth weight of children delivered in this situation ranged between 815 g and 2,083 g. Postnatal follow-up was not available for most of the reported babies. The number of brain dead mothers who were also organ donors is very few. Even fewer cases were associated with a successful delivery and organ donation. In the few cases where organ procurement was achieved, the graft survival has been reported to be excellent.

The extensive physiological changes associated with pregnancy coupled with the alterations that follow brain death, make the support of such patients technically challenging. The period of gestation beyond which support can be extended to the fetus has not been identified. From the data available so far, it seems that a fetus born before 24 weeks has a very poor outcome. Those born after 32 weeks seem to have a 98% chance of survival.

Cardiovascular support: Brain death is often associated with a period of tachycardia which resolves spontaneously. Maternal acidosis, hypothermia and myocardial dysfunction sometimes contribute to the slower heart rates. Reversal of these factors is essential to maintain a stable perfusing rhythm. Very few brain dead mothers are reported to be hypertensive. Invasive monitoring is recommended for hemodynamic optimization and titration of vasoactive agents. Nitroprusside is recommended to achieve control of hypertensive situations. However, the duration of therapy has to be strictly monitored to avoid untoward effects on the fetus. Aggressive fluid therapy, preferably with crystalloids, is recommended as initial strategy for hemodynamic stabilization. Low oncotic pressure states might warrant the use of colloids, but, starches might have to be consciously avoided to avoid toxicity to the kidneys. Dynamic indices of fluid responsiveness like extravascular lung water might help to prevent overloading the pregnant women and avoid generating pulmonary edema. The choice of vasopressor agent to maintain

by mansdocs.com

optimal blood pressure is not clear. Recognizing the endocrine effects of dopamine and the increase in myocardial oxygen demand it generates, it might be a safer decision to initiate nor-epinephrine as the first vasopressor. No data exists to suggest benefit or harm with epinephrine. The effect of epinephrine on lactate generation and glycemic status will have to be taken into consideration if this agent is used for hemodynamic support. It might be chosen as the first vasopressor in resource-limited set up and if the duration of support for the mother is likely to be short. The target mean arterial pressure in this subset of patients is above 80 mm Hg.

Respiratory support: Pregnancy is marked by a significant respiratory alkalosis. Since neuroprotection is not an issue of concern, target CO_2 levels can be set between 28–32 mm Hg. Monitoring end tidal CO_2 is recommended for these patients. Tidal volumes are preferably set between 6–8 mL/kg of ideal body weight. Respiratory rates and ratios may be appropriately set to achieve the CO_2 goals. Hypoxemia is a crucial determinant of fetal outcome. The maternoplacental unit is susceptible to hypoxemia at higher PaO_2 levels than in the nonpregnant state. Therefore, a PaO_2 greater than 70 mm Hg and an SpO_2 greater than 95% are recommended prior to delivery of the fetus. The same targets can be continued for preserving oxygenation of the potential organs to be harvested. There are several case series of pregnant women with ARDS who were supported by extracorporeal membrane oxygenation. Outcomes were reasonably good with fetal survival close to 70%. However, authors could not find mention of brain dead mothers who were supported by ECMO till delivery.

Endocrine support: Brain death is one clinical situation where endocrine support becomes a major determinant of good quality support for the victim. Diabetes insipidus (DI) is seen in close to three-quarters of patients. Early diagnosis is crucial. Early initiation of fluid resuscitation and vasopressin therapy is essential for effective reversal of the imbalances produced by DI. Hypothyroidism is known to set in very early in the situation of brain death. Appropriate correction of the biochemical values for the pregnant state needs to be made before supplementation can be initiated. Intravenous replacement is ideal wherever available. Adrenal insufficiency is also very common in brain dead patients. Methylprednisolone is the replacement of choice, since it does not cross the placental barrier. However, fetal lung maturity needs to be considered while deciding the choice of steroids in these patients. Hyperglycemia is known to be associated with brain death and needs to be controlled with insulin infusions.

Thermoregulation: Hypothermia is a constant feature in brain death victims. It could also be a marker of infection in the brain dead mother. Core temperature monitoring is ideal. Passive rewarming with fluids and warming blankets is recommended.

Nutritional support plays a crucial role in brain dead pregnant women as it does in other critically ill patients. The basal energy expenditure of a brain dead mother will be about 75% of the requirements in a normal pregnant state. Weight gain during pregnancy, fetal growth, maternal glycemic status and volume status should determine the strategy for route and content of nutritional support. Protein and fat requirements should be met as for a normal pregnant woman of that gestational age.

Infection control practices have to be meticulously followed in this subset of patients. Nosocomial pneumonia, blood stream infections and urinary tract infections are the most common nosocomial infections. Diagnosis has to be prompt and antibiotic strategy planned as per local microbiological data and sensitivity patterns.

Obstetric planning has to be charted in discussion with the concerned team. Cesarean section is the recommended route of delivery of the fetus. Lung maturity is the crucial determinant of strategy and outcomes.

The decision for organ harvesting has to be taken after the delivery of the fetus. The prolonged support for the mother would have made some of the organs marginal. But that should not preclude the assessment of each organ for appropriateness for harvest.

The ethical issues associated with prolongation of life of a brain dead woman are still open for debate. Sustaining the life of the mother to achieve fetal maturity might be contested by some. However, brain death as a marker of somatic death makes the rights of the fetus more significant than the "rights" of the mother. Moreover, using the maternal unit to support the fetus is itself described by some as a mode of organ donation. Advance directives are rarely available in this situation. A practical discussion with the family about the plan and priorities is crucial.

by mansdocs.com

SECTION 8

Pediatric Critical Care

by mansdocs.com

by mansdocs.com

CHAPTER

45

Recognition and Assessment of Critically Ill Child

Praveen Khilnani

INTRODUCTION

In outpatient practice pediatric specialist as well as general practitioner comes across common pediatric illnesses frequently. It is important to recognize potentially life-threatening conditions as well as conditions requiring immediate intervention and transfer to a higher level medical facility.

Besides accidental trauma, poisoning, insect bites, allergic reactions, common medical problems that bring the child to medical attention are fever, cough, respiratory distress, cyanosis, ear ache, poor feeding, vomiting, diarrhea, irritability, lethargy, convulsions and unresponsiveness. Common conditions that require immediate attention are—respiratory distress, shock, lethargy and coma.

Since our main goal as a medical practitioner is to prevent unnecessary mortality and morbidity by prompt and early recognition of potential problems leading to respiratory or cardiorespiratory arrest, it is important to pay attention to following during history and physical examination done simultaneously.

- Listen carefully to the mother.
- Do not ignore, it will not get better if something is not done.

Evaluate, Identify and Intervene

A carefully performed clinical assessment, including observation, history and physical examination, will detect serious illness with 90% sensitivity. Each component of the evaluation is effective in identifying serious illness.

The assessment of a seriously unwell child involves the following:

- Pediatric assessment triangle (PAT) (Initial impression, Fig. 1)
- Primary assessment (ABCDE assessment)
- Secondary assessment
  - Vital signs
  - Focused history
  - Detailed physical examination
- Diagnostic tests: Laboratory and radiological.

INITIAL IMPRESSION

It is the rapid assessment of a child with an emergency condition, through visual and auditory evaluation of the

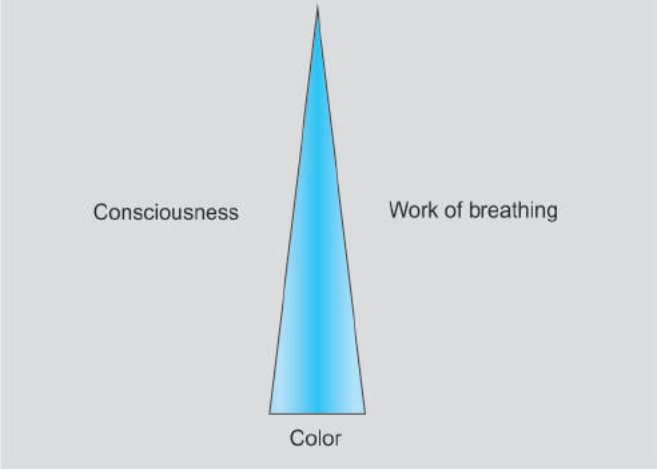


Fig. 1: Initial impression (pediatric assessment triangle).

by mansdocs.com

child's consciousness, work of breathing, and color. It is "from the door"—observation to be completed within seconds and no equipment is required. The initial assessment of the child's overall condition is of crucial importance. If the child exhibits abnormal findings, proceed immediately to the primary assessment part of evaluation.

Consciousness

- Reflects the adequacy of ventilation, oxygenation, brain perfusion,body homeostasis, and central nervous system function
- What is the child's state of consciousness: unresponsive, irritable, alert?
- Does the child look ill?

Work of Breathing

- Assess body position, visible movements of chest/abdomen and breathing pattern
- Listen for abnormal audible airway sounds (snoring, hoarse speech, grunting and wheezing)
- Look for visual signs of increased work of breathing such as abnormal position or posture (i.e. sniffing position, tripod position, head bobbing), retractions, nasal flaring, grunting, gasping and tachypnea
- Reflects the adequacy of airway, oxygenation and ventilation. Are the airways obstructed? Is the child short of breath?

Circulation to Skin

- Assess skin color
- Look at the skin and mucous membranes for abnormal color (pallor, mottling and cyanosis)
- Reflects the adequacy of cardiac output and perfusion of vitalorgans. Is the skin unusually pale, mottled or cyanotic?

The initial impression will help decide if the child problem is life threatening or not.

PRIMARY ASSESSMENT

It uses the ABCDE approach. During the evaluation primary assessment and management occur simultaneously. The primary assessment should be periodically repeated, particularly after major intervention or when a change in the patient's condition is detected (Evaluate-Identify-Intervene).

A: Airway

The goal is to assess if the airway is patent or if there are signs ofobstruction (e.g. stridor, dyspnea, hoarse voice). If the child is unresponsive and cannot talk, cry or cough,evaluate for possible airway obstruction. Is the airway noisy (e.g. snoring, stridor, wheeze, grunting or hoarse speech)? Determine if the airway is patent, and able to be maintained with positioning and suction, or not. If cervical spine injury is suspected,manually stabilize the head and neck in a neutral, inline position (jaw thrust without head tilt maneuver to open the airway).

Look in the mouth for blood, broken teeth, gastric contents and foreign objects. If solid material is visualized, remove it with a gloved finger coveredin gauze under direct vision. If a foreign body is suspected but not visualized, a combination of back blows and chest thrusts is recommended in infants. In an older child back blows in a forward leaning position is recommended. Abdominal thrusts in children are not recommended as their effectiveness and safety have not been established.

Insert an airway adjunct (e.g. oropharyngeal or nasopharyngeal airway, or laryngeal mask airway) as needed to maintain a patent airway. If airway patency cannot be maintained, perform tracheal intubation. Rapid sequence intubation (RSI) should be considered in all patients, except those in cardiac arrest, to provide optimum conditions and to minimize the potential for aspiration. Cricothyrotomy or emergency tracheostomy can be done as a last resort to maintain airway patency. Not many pediatricians would be familiar with performing these procedures, therefore in anticipation a consult should be obtained from an airway expert such as an anesthesia consultant or an ENT consultant.

B: Breathing

The goal in assessing breathing is to determine whether there is adequate gas exchange.

- Will the child lie flat? Is he in the tripod or "sniffing" position?
- Are accessory muscles being used (head bobbing in infants)? Or is there minimal movement of the chest wall?
- Is there sternal, supraclavicular, substernal, or intercostal recessionpresent?
- Is nasal flaring present?
- Is the respiratory rate fast, slow, or normal?
- Is cyanosis present?

by mansdocs.com

- Is air movement audible on auscultation?
- What is the oxygen saturation (SpO_2)?

Place your cheek near the child's face and mouth and feel/listenfor air movement and look at the chest/abdomen for respiratory movement. The child with breathing difficulty often has a respiratory rate outside the normal limits for their age, respiratory rate more than 60 in all children is abnormal. Initially the child becomes tachypneic, and as fatigue begins and hypoxia worsens, the child mayprogress to respiratory failure and bradypnea. On auscultation with a stethoscope over the mid axillary line, try to hear abnormal lung sounds (e.g. wheeze, crackles, snoring). Palpate thechest for tenderness, instability and crepitations.

Intervention

All children with breathing difficulties should receive high flow oxygen through a face mask oxygen as soon as the airway has been assessed and demonstrated to be adequate. Pulse oximetry is an excellent tool to use in assessing a child's breathing. A pulse oximetry reading more than 94% indicates that oxygenation is probably adequate. A reading less than 90% in a child with 100% mask oxygen could be an indication for assisted ventilation.

If the child is breathing adequately but is unresponsive, place thepatient in recovery position (lateral recumbent) after assessing ABCD with no other abnormal findings. If breathing is absent or the child is hypoventilating (slow respiratory rate or weak effort), respiration should be supported with oxygen via bag-valve-mask device and an airway adjunct needs to be inserted (eg. laryngeal mask airway, endotracheal tube).

C: Circulation

The goals are to assess adequate cardiovascular function and tissueperfusion, ensure effective circulating volume, and in trauma, controlof bleeding. Look for following points:

- Is skin color normal, or is it pale or mottled?
- Is there an increased respiratory rate without increased work of breathing?
- Is it cool peripherally but warm centrally?
- Is the pulse rate fast, slow, or normal?
- Is the pulse volume weak or strong?
- Is the capillary refill time (CRT) normal or prolonged?

It is important to determine the heart rate, pulse quality, skintemperature, CRT, and blood pressure (BP). Normal heart rate varies with age; tachycardia can be an early sign of hypoxia or low perfusion, but it can also reflect less serious conditions(e.g. fever, anxiety, pain). Bradycardia (rate <60/min. in children or <100/min. in newborns) indicates serious illness and poor myocardial perfusion.

Table 1: Acceptable 5th percentile of systolic blood pressure (BP) with age.

Age	*Systolic BP (mm Hg)*
Term Neonates (0–28 days)	< 60
Infants (1–12 months)	< 70
Children 1–10 years	70 + (age x 2)
Children > 10 years	< 90

Pulse quality reflects the adequacy of peripheral perfusion. A weak central pulse may indicate decompensated shock, and a peripheral pulse that is difficult to find, weak or irregular suggests poor peripheral perfusion and may be a sign of shock. Check the femoral pulse in infants and young children, or the carotid pulse in an older child or adolescent. If no pulse is felt, and there are no, or minimal signs of life, commenced cardiopulmonary resuscitation (CPR).

Next, evaluate the CRT, skin color and temperature. Normal CRT is less than 2 seconds. The CRT should be done centrally (e.g. on the chest) to minimize the impact of environmental factors. BP determination and interpretation can be difficult. Normal BP values in children vary according to age and are difficult to remember. Table 1 listing BP related to age can be very useful in clinical practice. A low BP indicates decompensated shock.

An easy formula for determining the lower limit of acceptable BP is: minimal acceptable systolic blood pressure = 70 + (2 × age in years).

BP trends are useful in determining the child's condition and response to treatment.

D: Disability (Mental Status)

Assess the patient by looking at appearance as part of Initial Impression and at level of consciousness with the AVPU (Alert, response to Verbal stimuli, response to Pain, Unresponsive) scale. The Pediatric Glasgow Coma Scale (GCS) is a second option (Table 2).

Evaluate the brainstem by checking the responses in each pupil to a direct beam of light. A normal pupil will constrict after a light stimulus. Evaluate the motor activity by looking for symmetrical movement of the extremities, seizures, posturing or flaccidity.

by mansdocs.com

Table 2: Glasgow coma scale.

Eye opening	
• Spontaneous	4
• Voice	3
• Pain	2
• None	1
Verbal	
• Oriented	5
• Confused	4
• Inappropriate	3
• Incomprehensible	2
• None	1
Motor	
• Obeys	6
• Localizes	5
• Flexor decorticate	4
• Decerebrate	3
• Extension	2
• Flaccid	1
• *Total maximum score*	15
• *Total minimum score*	3

- What is the child's AVPU score?
  - A: alert
  - V: responsive to voice
  - P: response to pain
  - U: unresponsive
- Is the child mobile? Or is there limited movement with poor muscle tone?
- If the child is crying or speaking, is this strong or weak?
- If crying, can the child be consoled?
- Does the child fix their gaze on the carer(s), or does he/she have a "glazed" appearance?
- Is the child's behavior normal for their developmental age?
- Is the child having convulsions, is he stiff or floppy?

With knowledge of the child's appearance from the initial appearance and AVPU scale, if the disability assessment demonstrates altered level of consciousness, begin with general life support/monitoring with oxygen, cardiac monitoring, and pulse oximetry. Intubation should be considered if GCS is less than 8.

E: Exposure

Proper exposure of the child is necessary for completing the initialphysical assessment. The initial impression using PAT requires removal of part of the child'sclothing to allow careful observation. Be careful to avoid rapid heatloss, especially in infants and children in a cold environment.

Table 3: Conditions requiring immediate intervention.

Airway	Complete/severe airway obstruction
Breathing	Apnea/significant work of breathing/bradypnea
Circulation	No detectable pulse/poor perfusion/hypotension/bradycardia
Disability	Unresponsiveness/depressed consciousness
Exposure	Hypothermia/bleeding/petechiae/purpura/abdominal distension

- Is there fever?
- Is there a nonblanching rash present?

SECONDARY ASSESSMENT

The secondary assessment focuses on advanced life-support interventions and management. It is important to perform an additional assessment with a focused history and physical examination in stable patients. Generally, the initial assessment is aimed at detecting immediate life-threatening problems that can compromise basic life functions, as in the primary survey.

The secondary survey is intended to detect less immediate threats to life and has several specific objectives:

- Obtaining a complete history, including mechanism of injury or circumstances of the illness.
- Performing a detailed physical examination
- Laboratory and radiological diagnostic testing
- Establishing a clinical diagnosis
- Obtain a quick random blood sugar
- Performing laboratory investigations and imaging.

ONGOING ASSESSMENT

Always reassess the patient; the purpose is to assess the effectiveness of the emergency interventions provided and identify any missed injuries or conditions. This should be performed in every patient after the detailed physical examination and after ensuring completion of critical interventions (Table 3).

Categorization by Severity—Respiratory Distress

- Tachypnea
- Tachycardia

by mansdocs.com

- Increase respiratory effort
- Abnormal airway sounds
- Pale cool skin
- Changes in mental status.

Respiratory Failure

- (Early) Marked tachypnea/tachycardia
- (Late) Bradypnea, apnea/bradycardia
- Increased/decreased/no respiratory effort
- Cyanosis
- Stupor/coma.

Categorization by Severity

- Shock
- Compensated
- Tachycardia
- Cool pale diaphoretic skin
- Delayed CRT
- Weak peripheral pulses
- Narrow pulse pressure
- Oliguria.

Hypotensive

- All features of compensated shock and BP below the 5th percentile
- Change in mental status.

Initial Stabilization

Things required at all practice locations (hospital or private practice clinic):

- Oxygen source and mask
- Bag mask valve device (Ambu)
- Laryngeal mask airway
- Intubating equipment
- Intraosseous needle
- Intravenous (IV) cannula, IV fluids
- Suction
- Pulse oximeter
- Nebulizer

Common Initial Interventions

Once the critically ill child is recognized, do not waste time in detailed investigations and diagnosis.

Do the following regardless of diagnosis:

- Start oxygen
- If respiratory distress
  - Ensure airway open by head tilt-chin lift jaw thrust
  - If not maintainable intubate.
  - If can not intubate ventilate with bag and mask

If cannot intubate or ventilate, then use laryngeal mask airway and call the best expert in airway management.

Foreign Body Obstruction

If known Foreign Body Obstruction

- Then back blows, chest thrust and Heimlich maneuver
- Nebulize as required (adrenaline or beta 2 stimulant).

Monitor Oxygen Saturation If Pulse Oximeter is Available

Shock

- Establish IV/intraosseous access.
- Do not waste more than 90 seconds trying for IV access or wasting time with attempting to place a central line.
- Intraosseous access can be used in all age groups.
- Push fluid bolus 20 mL/kg up to 60–80 mL/kg of isotonic fluid (Normal saline/Ringers lactate)
- After each intervention reassess airway breathing and circulation (capillary refill, color, heart rate, pulse, BP, mental status, urine output)
- Other supportive therapy.

First Dose of Antibiotic

Anticonvulsants: If convulsions use diazepam IV/rectal, lorazepam or midazolamiv (Caution: respiratory depression/arrest)

- Phenytoin/Phenobarbitone intravenously.

Fever control

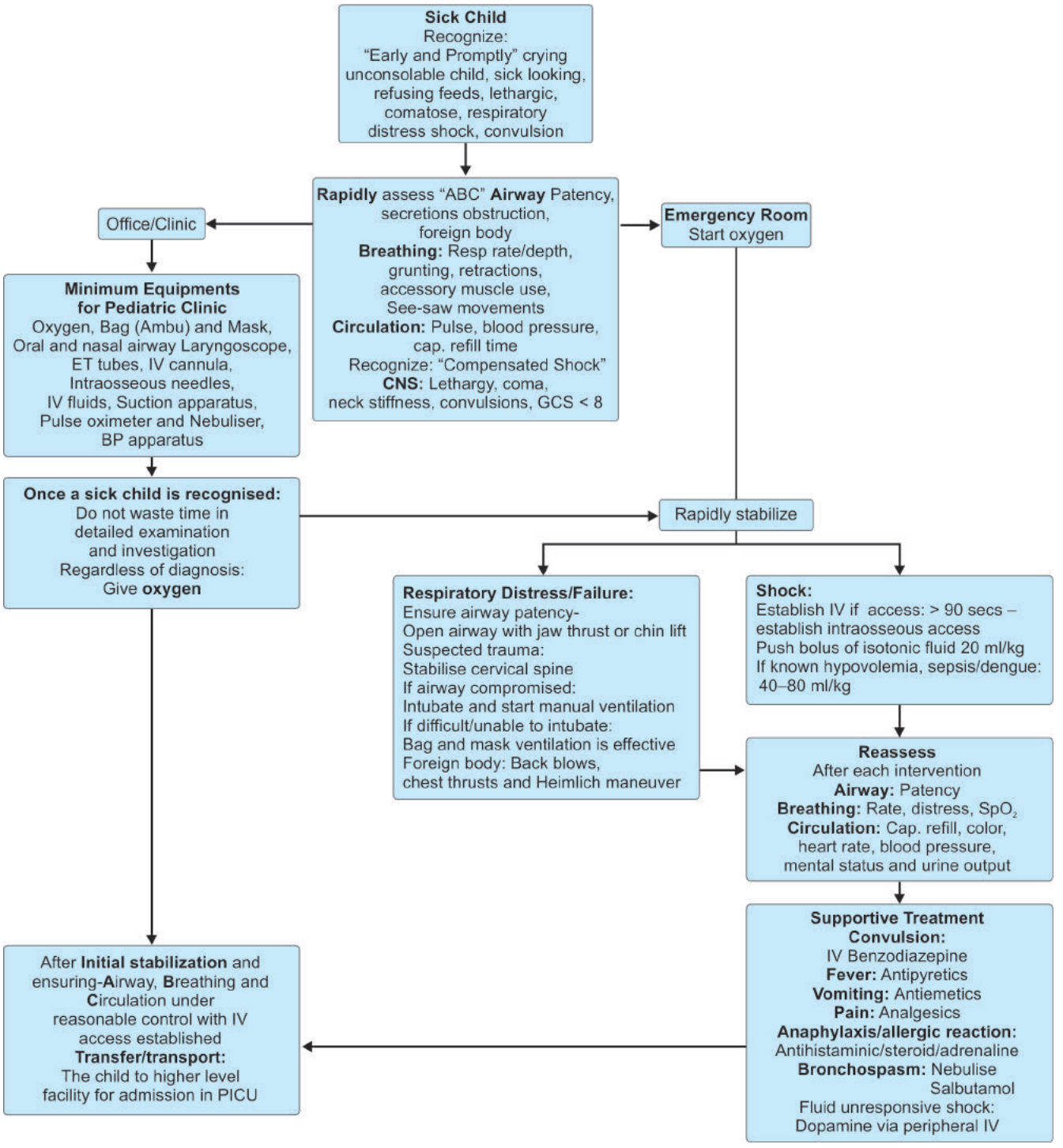
- *Analgesics, if severe pain*: Nonsteroidal anti-inflammatory agents/narcotics as necessary
- *Antiemetics*: If vomiting
- *Antiallergics*: If allergic reaction/anaphylaxis subcutaneous adrenaline, antihistaminics, steroids.

Transport

After initial stabilization and ensuring airway, breathing and circulation under reasonable control with established IV access, transfer/transport to a higher level facility needs to be arranged.

by mansdocs.com

Flowchart 1: Approach to critically ill child.



Take Home Message

- Solve immediate problem.
- Do not waste time in establishing precise diagnosis
- Recognize critical illness
- Stabilize
- Arrange transfer to a pediatric intensive care unit
- Ensure continued stabilization measures until care is handed over.

by mansdocs.com

CHAPTER

46

Pediatric Septic Shock

Saptharishi LG, Sunit Singhi

INTRODUCTION

Septic shock is a common presentation in the pediatric emergency room (ER) and is one of the most common causes of mortality in pediatric intensive care units (PICU). According to 2008 World Health organization (WHO) data, nearly 70% of the estimated 8.8 million under-five children deaths are caused by pneumonia, diarrhea, malaria and measles. Septic shock and severe sepsis are the usual culminating events in these children. A multicenter study from Columbia estimated that more than half of all admissions with severe sepsis were younger than 2 years and they are at especially high risk of septic shock.

A rational approach to the child presenting in shock not only requires a thorough understanding of the dynamic nature of shock, but also warrants early recognition, hemodynamic monitoring and use of specific strategies to combat the shock syndrome.

PATHOPHYSIOLOGY

"Shock" is the clinical expression of acute circulatory dysfunction and consequent failure to deliver sufficient oxygen and other nutrients to tissue beds. The critical event is poor perfusion of vital organs and other tissues and consequently altered cellular and subcellular metabolism, and energy production. At the cellular level, there is decrease in adenosine triphosphate (ATP) synthesis and subsequent anaerobic metabolism and cytotoxic metabolite accumulation.

CLINICAL PROGRESSION OF SEPTIC SHOCK

The clinical manifestations of sepsis and septic shock are as a result of complex interplay between microbial product and host mediator systems. The response to severe sepsis in children is distinctly different from that in adults. The presentation depends on the degree to which systemic vascular resistance (SVR), myocardial contractility and heart rate (HR) are affected.

Septic shock can have three patterns of clinical presentation. In nearly 20% of children, SVR are decreased associated with an increase in cardiac output (CO). These children show a decrease in diastolic pressure with low cardiac filling pressures, tachycardia, bounding pulses, wide pulse pressure, flash capillary refill and decreased oxygen consumption (*warm shock*).

Nearly 60% children present with increased SVR as a compensatory mechanism with preferential diversion of blood away from nonvital vascular beds like skin, gut, etc. CO is decreased either due to impaired myocardial function of increased afterload. Clinically, this presents as weak peripheral pulses, mottled or pale skin color with delayed capillary refil (*cold shock*), and these children may have normal or rarely supranormal blood pressure (compensated shock). In the third variety, both CO and SVR are decreased with clinical presentation fitting into neither warm nor cold shock.

Irrespective of the initial presentation, as the shock progresses, there is increase in anaerobic metabolism, hyperlactatemia and release of proteolytic/vasoac-

by mansdocs.com

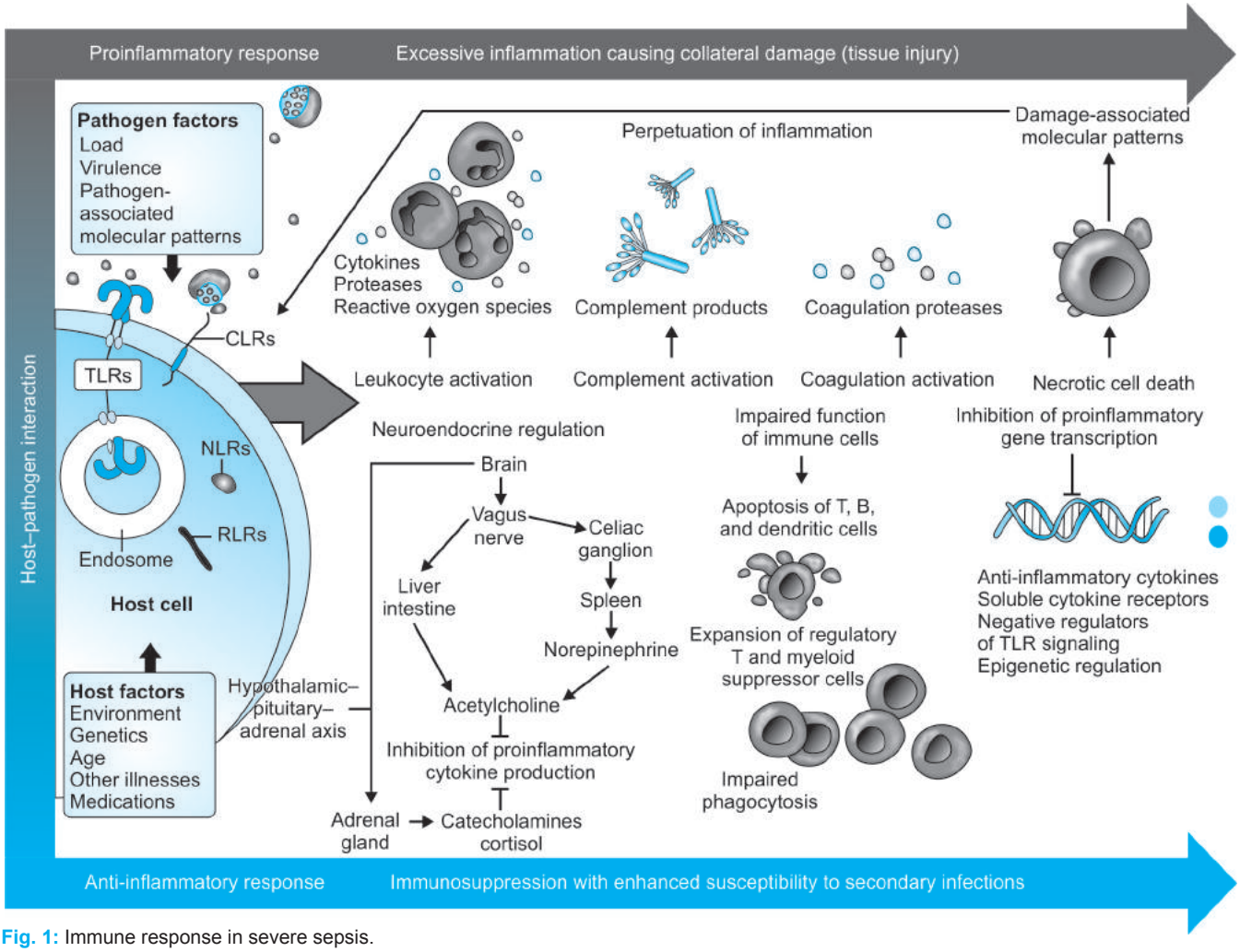


Fig. 1: Immune response in severe sepsis.
(CLRs: C-type lectin receptors; NLRs: Nucleotide-binding oligomerization domain-like receptors; RLRs: RIG-like receptors).

tive substances. Platelet aggregation and release of tissue thromboplastin produce hypercoagulability and disseminated intravascular coagulation (DIC). The prolonged hypoperfusion of brain, heart, kidneys and lungs leads to ischemic injury to these organs with progressively worsening coma, renal failure and acute respiratory distress syndrome (ARDS). A generalized endothelial damage disrupts the integrity of cell membrane with unrestrained shifts in fluids and electrolytes. There is leakage of fluid to interstitium (so-called "third-space") and maldistribution of the blood volume. The end result of all this is multi-organ dysfunction syndrome.

IMMUNITY IN SEPTIC SHOCK

In response to a severe infection (Fig. 1), when a sufficiently severe proinflammatory insult occurs, patients typically experience a constellation of vital sign and laboratory changes termed the systemic inflammatory response syndrome (SIRS). In the most severe cases of hyperinflammation, patient can progress to septic shock and organ dysfunction. The acute morbidity and mortality result from the overwhelming systemic immune response. Exaggerated proinflammatory response leads to tissue destruction and necrotic cell death with release of more "danger" molecules (Fig. 1).

Soon (usually less than 24 hours), compensatory mechanisms come into play and shutdown the immune system's proinflammatory response through the induction of anti-inflammatory cytokines. This phenomenon is referred to as the compensatory anti-inflammatory response syndrome (CARS). Although a transient CARS state is necessary to regulate and protect against

by mansdocs.com

inflammatory injury like SIRS, it must be also regulated. A persistent, severe form of a CARS leads to an immunoparalysis state. Such find themselves at increased risk for development of nosocomial infection and death.

The extent and duration of these opposing reactions are determined by both host and pathogen factors. Inflammatory response is initiated by interaction between pathogen-associated molecular patterns (PAMPs) on pathogens with toll-like receptors (TLRs) and similar molecules. The host's mediator pathways that have been implicated in the pathogenesis of septic shock include components of coagulation cascade, complement and kinin systems as well as factors released from stimulated macrophages and neutrophils, like cytokines, tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1), vasoactive peptides (histamine) and products of arachidonic acid metabolism (eicosanoids).

DEFINITIONS AND SEVERITY OF SEPSIS

The definitions for SIRS, sepsis and related terms as described in Surviving Sepsis Campaign 2012 are provided in Box 1. The PIRO score, which describes sepsis as a multidimensional construct with predisposition, infection, response to infection and organ failure stages, aims to make severity of sepsis assessment more objective. It has been well studied in adults. However, validity of PIRO approach has not been established in children.

Box 1: Definition of sepsis and related terminology.

Systemic Inflammatory Response (SIRS): In presence of fever or hypothermia with tachycardia, tachypnea and leukocytosis, the presence of at least two of the four criteria is necessary, one of which must be abnormal temperature or leukocyte count:

- *Core temperature of >38.5°C or <36°C*
- *Tachycardia*, defined as a mean heart rate >2 SD above normal for age [in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5–4 hour time period] *or for children <1 year old: bradycardia*, defined as a mean heart rate <10th percentile for age (in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5 hour time period)
- *Tachypnea* (mean respiratory rate >2 SD above normal for age) or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
- *Leukocytosis* or *leucopenia* (total count elevated or depressed for age, not secondary to chemotherapy-induced leukopenia or >10% immature neutrophil).

Sepsis: SIRS with a suspected or proven infection (by positive culture, tissue stain, or polymerase chain reaction test) caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Severe sepsis: Sepsis with evidence of altered organ hypoperfusion and dysfunction, such as altered mental status, oliguria or increased lactate. SIRS with any one of the following (equivalent of sepsis-induced tissue hypoperfusion):

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output <0.5 mL/kg/h for more than 2 hours despite adequate fluid resuscitation
- Acute lung injury with PaO_2/FIO_2 <250 in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FiO_2 <200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dL (176.8 μmol/L)
- Bilirubin >2 mg/dL (34.2 μmol/L)
- Platelet count <100,000 μL
- Coagulopathy (international normalized ratio >1.5)

Septic Shock: Sepsis and cardiovascular organ dysfunction, where *cardiovascular dysfunction* is defined as presence of any of the following despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hour:

Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age *or* need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/minute or dobutamine, epinephrine or norepinephrine at any dose) *or* two of the following:

- *Unexplained metabolic acidosis*: Base deficit >5.0 mEq/L
- Increased arterial lactate >2 times upper limit of normal
- *Oliguria*: urine output <0.5 mL/kg/h
- Prolonged capillary refill >5 seconds
- Core to peripheral temperature gap >3°C

(SD: Standard deviation; PaO_2: Partial pressure of oxygen; FIO_2: Fraction of inspired oxygen; BP: Blood pressure).

by mansdocs.com

Table 1: Investigations in a child with septic shock.

S. No	Organ system	Investigations
1.	Cardiovascular system	Chest X-ray, blood gases, ECG, echocardiogram, arterial lactate, mixed venous oxygen
2.	Gastrointestinal system	Gastric pH, sublingual pH, serum bilirubin levels, liver function tests, stool occult blood
3.	Respiratory system	Blood gases, chest X-ray, lung function tests
4.	Renal system	Urine color, specific gravity, urinalysis, urine sediments, urea, creatinine, early AKI biomarkers (if available)
5.	Metabolic	Serum Na, K, Mg, ionized calcium, blood glucose, base excess, anion gap, serum albumin
6.	Hematological system	Complete blood counts with differential counts, coagulation profile, FDP, D-dimers, etc.
7.	Sepsis work-up	C-reactive protein, blood culture, procalcitonin, other body fluid cultures, etc.

(AKI: Acute kidney injury; ECG: Electrocardiogram; FDP: Fibrin degradation product).

EARLY RECOGNITION OF SEPTIC SHOCK

To apply aggressive therapeutic interventions, early recognition of shock is crucial. No single clinical finding or laboratory test is diagnostic. But, reducing the time of diagnosis of severe sepsis and septic shock is thought to be the most critical component in reducing mortality. The Pediatric Assessment Triangle (PAT) of the AAP-PALS (American Academy of Pediatrics- Pediatric Advanced Life Support) can be a useful tool in identifying children at risk for, as well as those in septic shock. Protocolized, emergent, quantitative fluid resuscitation of patients with sepsis-induced tissue hypoperfusion decreases mortality from 40% to 12%.

It may be challenging to identify signs of tissue hypoperfusion in a febrile, irritable infant. Fever, tachycardia and vasodilation are common in children with any infection. Septic shock has to be suspected when children with this triad develop clinical signs of inadequate tissue perfusion (altered sensorium/decreased urine output (UOP) or abnormal capillary refill—delayed or flash). The color, temperature and appearance of a child's skin can be a vital clue. As discussed previously, hypotension is not essential for the diagnosis of septic shock.

In children, tachycardia occurs early and is the sole determinant of CO. True tachycardia is noticed well before any notable alterations in blood pressure. Decreased tissue perfusion can be identified by decreased surface temperature, impaired capillary refill (>2 seconds) and impaired function of several organs. Cold extremities or increased peripheral core temperature gradients (>2°C indicates early shock. Capillary refill time (CRT) greater than 3 seconds is clearly abnormal and a sensitive indicator. Serial determination of CRT at frequent intervals is an excellent indicator of response to treatment. "Vital organ hypoperfusion" can be assumed to occur if oliguria from renal hypoperfusion coexists, or if child develops impairment sensorium with disorientation, lethargy, etc.

LABORATORY TESTING

Certain laboratory parameters should be obtained for every child with septic shock and a few, as warranted by the patient's condition and suspected etiology. Directing laboratory investigations to assess the functioning of individual organ systems as shown in Table 1 is a useful practical approach. Leukocytosis is less predictive for presence of sepsis in a fully immunized child. C-reactive protein (CRP) and procalcitonin can be useful in identification of underlying sepsis, when combined with clinical data.

MONITORING PARAMETERS IN PEDIATRIC SEPTIC SHOCK

Frequent or continuous monitoring involving careful, repeated observations by a competent pediatrician is most valuable. Bedside parameters that must be monitored include HR, systolic blood pressure (SBP), mean arterial pressure (MAP), UOP, peripheral perfusion—CRT, pulse volume and character, respiratory rate and pattern and level of consciousness.

Monitoring blood lactate can give an indication of efficacy of therapies that improve perfusion; establishment of effective perfusion with fluid resuscitation generally improves early lactate clearance (decrease of 10%). Lactate levels are useful for diagnosis, titrating management as well as prognostication in adults and may be useful in pediatric septic shock as well.

by mansdocs.com

Cardiac output monitoring allows for the important discrimination between a low output and a high output hyperdynamic state. Intensivist-performed bedside ultrasonography and transthoracic echocardiography are simple, safe and easily repeatable at bedside. Echocardiographic monitoring of inferior vena caval (IVC) diameter and cardiac contractility, both diastolic filling and systolic function (ejection fraction) are helpful in determining fluid responsiveness, and to guide the vasoactive therapies. IVC collapsibility index (in a spontaneously breathing child) and distensibility index (in a child on positive pressure ventilation) have been found useful in predicting fluid responsiveness. Among spontaneously breathing patients without vasopressor support, the maximal inferior vena cava diameter seems to be a more robust estimate of central venous pressure (CVP) than the IVC collapsibility index or the internal jugular vein aspect ratio.

Passive leg raising (PLR) test can be a useful test in children to predict fluid responsiveness (Lukito et al.). Cardiac index decrease by greater than 10% induced by PLR predicted preload-dependent status with sensitivity of 55% and specificity of 85%.

Among invasive techniques, the role of CVP, its accuracy and its role in estimating fluid responsiveness in children is being increasingly questioned. CVP does not predict fluid responsiveness accurately and only poorly reflects preload in children. Newer studies and detailed reviews on CVP have shown it to be not very useful in guiding fluid therapy during resuscitation in septic shock. This is attributable to the fallacies in the available CVP monitoring techniques and their inability to measure other factors that determine venous return.

Directing therapies to a goal of *superior vena cava/mixed venous oximetry* ($ScvO_2$) saturation greater than 70%, Oliveira et al. observed a mortality reduction from 39% to 12% in children with septic shock. A more accurate assessment of perfusion can be achieved by combining $ScvO_2$ with CO measurement or lactate levels.

Invasive arterial pressure monitoring-based pulse pressure variations (PPV) are a reliable indicator of fluid responsiveness in adults but specific cut-off values have not been established. Reliability of arterial pressure variations decreases with spontaneous respiration, nonsinus rhythm, pulmonary hypertension, right heart failure, low tidal volume or open-chest conditions. Of the other methods to assess CO, thermo-dilution measurement requires a pulmonary artery catheter and bioimpedance methods are not yet reliable in children.

MANAGEMENT OF SHOCK

The major treatment objective is rapid reversal of tissue hypoperfusion and thus, prevention of all its sequelae. The active critical chain method (ACCM) algorithm (PALS recommended) implementation has reduced mortality and morbidity related to septic shock.

Airway and Oxygen

The initial resuscitation involves securing patent-airway, administration of oxygen using face mask oxygen, or if needed, high flow nasal cannula or nasopharyngeal CPAP. In general, oxygen should be administered initially to all patients in shock and arterial oxygen saturation of 92% or higher should be targeted. The decision to intubate and ventilate should be taken early based on clinical assessment.

Intravenous Access

Emergency intravenous access during the first 2 minutes, via cannulation of peripheral vein with short catheters is preferred; however, if there is difficulty, intraosseous route could be life saving. Stress on placement of a central catheter during resuscitation is decreasing.

Fluid Resuscitation

Early rapid fluid resuscitation is fundamental to survival in septic shock. Preload needs to be optimized to improve CO and thus oxygen delivery. Recent evidence clearly support the use of crystalloid (normal saline) in pediatric septic shock. In hypotensive patients, fluids should be given as rapidly as possible using rapid pull-push or a pressure bag system. In patients with normal blood pressure, fluids should be given in aliquots of 20 mL/kg over 15–20 minutes. Children with septic shock usually require 40–60 mL/kg, in the first hour of resuscitation.

Patient should be monitored for clinical signs of myocardial dysfunction or pulmonary edema during fluid therapy. The tendency to develop pulmonary edema and capillary leak during administration of large volume of fluids during resuscitation may be countered by providing ventilation using self-inflating or flow-inflating ventilation bags in the ER. An attempt should be made to achieve all the therapeutic end-points. Discontinuing fluid therapy based on achievement of some but not all the goals results in inadequate resuscitation.

by mansdocs.com

Clinical indicators of excessive fluid resuscitation include pulmonary rales on auscultation, pink, frothy sputum, palpable liver edge, increased jugular venous pressure, S3 gallop and a decrease in SpO_2. If these signs are noted, further fluid administration is interrupted briefly for endotracheal intubation. Since shock can worsen during or following intubation, initiation of an appropriate inotrope infusion often improves the safety profile of this procedure. Following intubation and positive pressure ventilation, features of pulmonary edema and hepatomegaly usually resolve/improve while shock persists. Further fluid aliquots of 10–20 mL/kg over 10–20 minutes are recommended until shock resolves or pulmonary edema and hepatomegaly recurs.

Cardiovascular Support

Following adequate intravascular volume repletion, continued presence of hypotension and/or poor perfusion (fluid refractory shock) warrants the consideration of vasoactive therapy, which should be goal directed. Begin dopamine infusion at 10 µg/kg/minute by intravenous route. Reverse cold shock by titrating dopamine, or if resistant (normal or low blood pressure) add epinephrine (0.05–0.3 µg/kg/minute).

Reverse warm shock with wide pulse pressure by using norepinephrine. Children with warm shock may do well with vasopressors alone. In all situations, optimal preload is essential before vasoactive therapy is contemplated. Children with septic shock more often have myocardial dysfunction and low CO even early in illness; hence, it is preferable to combine inotrope with a vasopressor. Dopamine (10–20 µg/kg/minute) can be used as first- line drugs for giving this kind of support.

Late stages of septic shock may have significant impairment of myocardial function. Therapy is directed towards increasing myocardial contractility and decreasing left ventricular afterload. In such situations, inodilators like milrinone are preferred if child is normotensive. If child is hypotensive, optimize preload with optimize blood pressure with sympathomimetics before initiating milrinone (Box 2).

Patients with low CO state (myocardial failure) despite adequate fluid resuscitation require inotropy. Dobutamine (5–20 µg/kg/minute) is the *agent of choice for inotropic effect*. However, dobutamine alone may be inadequate in a hypotensive patient. Therefore, dobutamine (inotrope) is usually combined with a vasopressor such as dopamine or norepinephrine to increase the peripheral vascular resistance. The low CO state, characterized by persistent narrow pulse pressure and/or prolonged capillary refill, even after use of dopamine, may also be improved with addition of dobutamine (up to 20 µg/kg/minute) or low-dose epinephrine (<0.3 µg/kg/minute).

Box 2: Categories of septic shock in children.

- *Fluid-refractory/dopamine-resistant shock*: Shock persists despite 60 mL/kg or more fluids in the first hour and dopamine infusion >10 µg/kg/minute
- *Catecholamine resistant shock*: Persistent cardiovascular dysfunction despite the administration of at least 60 mL/kg of intravenous fluid resuscitation in the first hour and maximum dopamine or norepinephrine or epinephrine therapy
- *Refractory shock*: Shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid and hydrocortisone) homeostasis.

When a child in septic shock does not improve and the goals of treatment are not achieved even after dopamine and or dobutamine infusion, the shock is labeled as *fluid refractory, dopamine/dobutamine resistant shock*. Dopamine resistant shock may reverse with epinephrine or norepinephrine infusion. The dose should be titrated to minimum required for the desired effect; higher doses cause severe vasoconstriction, splanchnic ischemia and lactic acidosis. Further management should be based on the algorithm depicted in Figure 2.

End-Points

Reversal of hypoperfusion, hypotension and end-organ dysfunction (normal UOP/mental status) are early priorities; optimizing CO is next priority. Early goal-directed therapy aimed at achieving a CVP 8–12 mm Hg, normal mean blood pressure, normal UOP and a central (superior vena cava) or mixed venous oxygen saturation greater than or equal to 70% has made a significant impact on survival from septic shock in adults and children (Box 3).

MULTI-PRONGED SEPSIS CONTROL STRATEGY

Source Control and Antibiotics

Therapy with appropriate antibiotics in appropriate dose should be initiated in all cases suspected of septic shock (preferably, after cultures are obtained) within the first hour. It is preferable to provide empirical broad spectrum

by mansdocs.com

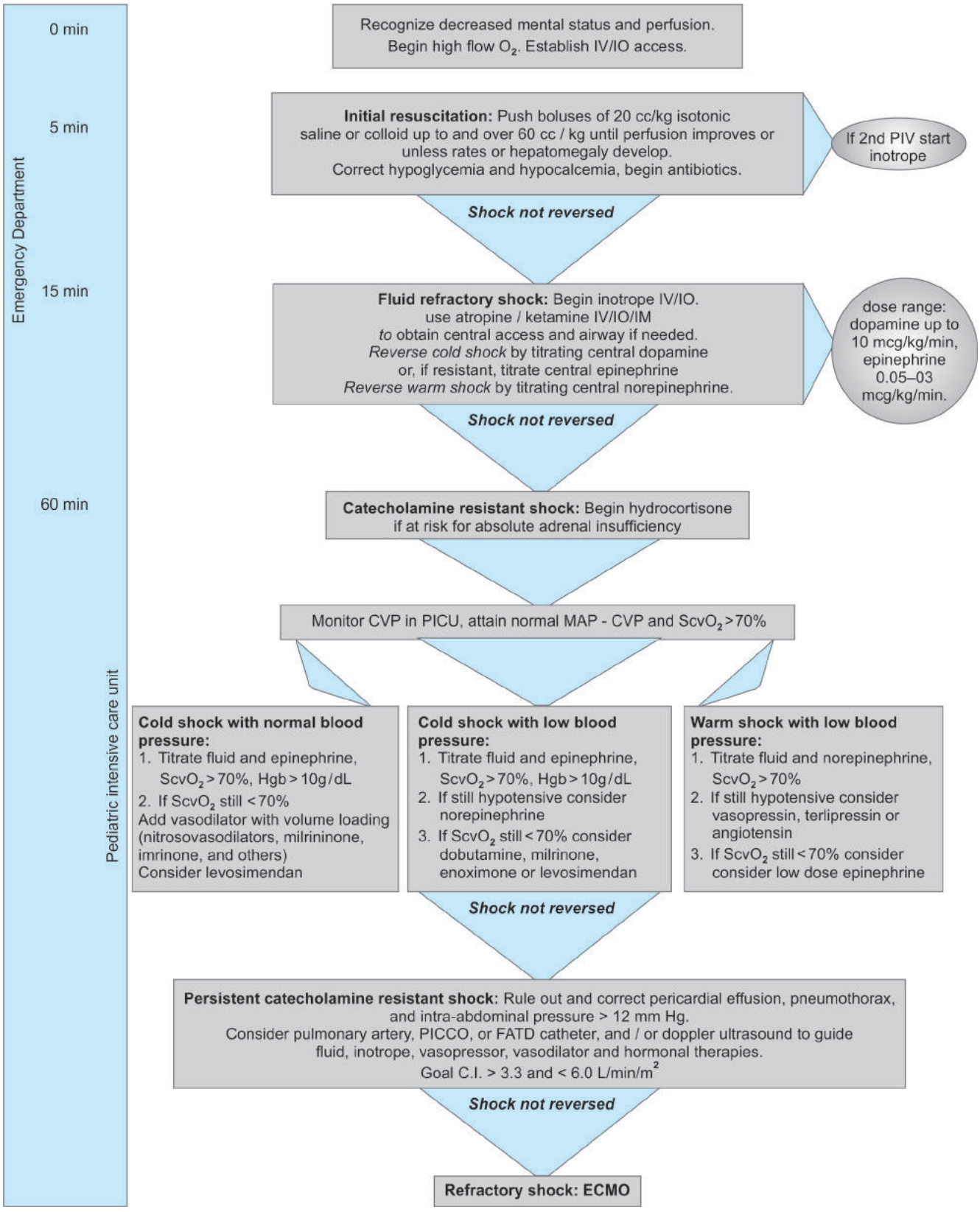


Fig. 2: Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children.

by mansdocs.com

Box 3: Initial therapeutic end-points of resuscitation of septic shock.

- Capillary refill ≤2 seconds
- Normal blood pressure for age
- Normal pulses with no differential
- Warm extremities
- Urine output >1 mL/kg/h
- Normal mental status
- $ScvO_2$ ≥70%
- Cardiac Index 3.3–6 L/min/m^2

($ScvO_2$: Mixed venous oximetry saturation).
Source: Modified from Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41: 580-637.

antibiotic coverage taking into consideration, primary site of infection, local bacterial sensitivity pattern and immunocompetence of the host. In addition, aggressive measures need to be carried out for removing foci of infections, such as abscesses, collections or pus pockets.

Correction of Metabolic Derangements

Acidosis

A significant secondary complication of shock is the development of high anion gap metabolic acidosis (lactic acidosis). Acidosis, usually improves with reversal of the low perfusion state. However, presence of severe acidosis per se impairs metabolic processes, impedes normal neurovascular interactions and prevents effective pharmacologic actions of vasoactive agents. Correction of metabolic acidosis is indicated when pH less than 7.15 with bicarbonate less than 8 mEq/L. Correction is initially given as a rescue bicarbonate of 1–2 mEq/kg followed by a gradual correction. Care must be taken to avoid over correction as this may impair cardiac function and cause paradoxical acidosis. There is no consensus on either timing or appropriateness of threshold for administration of sodium bicarbonate during resuscitation in children with septic shock.

Glucose

At the time of resuscitation, hypoglycemia is of major concern for its negative inotropic effect and associated severe neurological damage. It should be identified rapidly and corrected immediately. It may be treated with 5 mL/kg of 10% dextrose solution or 2 mL/kg of 25% dextrose solution. A regular monitoring protocol should then follow to maintain normal blood sugar, subsequently. Hyperglycemia should be treated with insulin therapy and frequent (2 hourly) blood sugar monitoring after initial resuscitation is over, if levels are above 180 mg/dL or if it is associated with polyuria. Intensive insulin therapy, however, is not recommended to achieve strict glycemic control in sepsis; there is no definitive evidence to support it in children.

Hypocalcemia

Ionized hypocalcemia is common in neonates and infants with sepsis admitted to PICU and may be a reversible contributor to cardiac dysfunction and hypotension. Administration of calcium in septic patients with ionized hypocalcemia (<4.2 mg/dL) may improve blood pressure. However, there is no evidence to suggest a survival benefit. A dose of calcium (1–2 mL/kg of 10% calcium gluconate solution by infusion) may be given empirically before labeling septic shock as dopamine-resistant shock.

Temperature Regulation

A recent trial has shown early shock reversal and decrease in early mortality with normothermia, achieved by external cooling (36.5–37°C). Further studies are required to study the impact of temperature regulation in pediatric septic shock.

Respiratory/Ventilatory Support

Respiratory muscles and the work of breathing consumes significant amount of energy (CO) in child in shock. Therefore, patients in shock should be intubated early and treated with positive pressure ventilation. Indications for mechanical ventilation in the management of a patient in shock are:

- Apnea or ventilatory failure (acute respiratory acidosis)
- Inadequate oxygenation with high-flow delivery devices
- Increased work of breathing with high risk of fatigue
- Frank features of pulmonary edema/fluid overload.

During mechanical ventilation, lung-protective strategies are to be employed with target tidal volumes of 6–8 mL/kg. Fraction of inspired oxygen (FiO_2) needs to be kept at or below 0.6 by judicious use of positive end expiratory pressure (PEEP). PEEP may compromise venous return and warrant fluids.

by mansdocs.com

Cerebral Protection

Early correction of hypoxia, hypoglycemia and cerebral edema should be given full attention. Central nervous system (CNS) infection should be actively excluded, if necessary, by cerebrospinal fluid (CSF) examination and computed tomography (CT) scan. Hyponatremia should be looked for, and if present, should be corrected cautiously. Good CO should be maintained as cerebral blood flow is correlated with cardiac index in septic shock.

Renal Salvage/Replacement

The hypotension and hypoperfusion associated with shock state affects renal perfusion pressure and may often lead to renal failure. Aggressive fluid replacement is necessary to support UOP. Nevertheless, should hyperkalemia, refractory acidosis, hypervolemia and altered mental status occur, dialysis (peritoneal/slow low-efficiency dialysis) should be seriously considered. Administration of nephrotoxic drugs should be avoided.

Gastrointestinal Support

Gastrointestinal disturbances after shock include stress bleeding and ileus. Ileus may result from hypokalemia and may lead to abdominal distension with respiratory compromise. Stress ulcer and gastrointestinal blood loss can be prevented by using antacids, sucralfate and/or hydrogen (H_2) receptor blockers or proton pump inhibitors (PPIs). Initiation of enteral feeding should be done as early as feasible.

Hematological Support

The ACCM guidelines recommend blood transfusions for hemoglobin less than 10 g/dL and if central venous oxygen saturation (SVO_2/$ScvO_2$) of 70% is not achieved during the acute resuscitation phase. Data suggest that a hemoglobin level of 7 g/dL as transfusion, trigger may be safe subsequently, for stabilized children with sepsis. In conclusion, restrictive strategies are preferable to liberal transfusion strategies.

Disseminated intravascular coagulation frequently complicates shock. The use of fresh frozen plasma to correct laboratory clotting abnormalities is not recommended. These should be used only if there is bleeding or if an invasive procedure is planned. *Platelets transfusion* is recommended when counts are less than 5,000/mm^3 regardless of bleeding or if there is bleeding and counts are less than 40,000/mm^3.

Nutritional Support

Excessive catabolism with destruction of lean body mass is the most common nutritional abnormality in shock states. Early enteral nutrition is more physiological and preferred. Close monitoring of daily caloric intake and determination of serum albumine, electrolytes and liver function tests should be done. Addition of vitamins and essential trace metals is important. Bower et al. found decrease in rate of infectious complications and length of hospital stay with immune enhancing diets, but further research is needed before they can be recommended for routine use in septic shock.

Corticosteroids Therapy

Although adrenal insufficiency (absolute/relative) is common in children with severe sepsis and septic shock, corticosteroids are recommended only in patients with proven or suspected adrenal insufficiency. Corticosteroids are also recommended for catecholamine-resistant septic shock in children. The recommended dose varies between hydrocortisone 1–5 mg/kg/day, though children in the *resolve* study, who received steroids had no improvement in morbidity or mortality. At present, there is insufficient evidence to determine role of low dose hydrocortisone in children with septic shock.

Intravenous Immunoglobulins

It is known that intravenous immunoglobulins (IVIG) can neutralize endotoxins and attenuate the overshooting inflammation in patients of sepsis. There is no clear evidence, however, that it has benefits in children. Large clinical trials and recent consensus guidelines do not recommend use of IVIG in patients with severe sepsis or septic shock.

Anti-inflammatory and Immunotherapy

Though numerous adjunctive therapies have been advocated for children with pediatric septic shock, none have been proven useful in all children, to be recommended for routine use. The interventions considered include ibuprofen, pentoxifylline, immunoglobulins, endotoxin antibodies, TNF antibodies, IL-1ra, platelet activating factor (PAF)-antagonists, bradykinin antagonists, etc.

by mansdocs.com

CATECHOLAMINE REFRACTORY SHOCK

A meticulous search for the causes of persistent catecholamine-resistant shock should be made if therapeutic goals are not achieved in spite of adequate volume loading and high doses of appropriate vasoactive agents. One must rule out mechanical causes of catecholamine-resistant shock such as impaired drug delivery, etc. Other causes of refractoriness include "6 Hs and 5 Ts"—hypoxia, hypovolemia, hypoglycemia, acidosis, hypocalcemia, hypo/hyperkalemia, cardiac tamponade, tension pneumothorax, coronary or pulmonary thrombosis, toxins, etc. If shock remains refractory, despite correction of all the above factors, putting the child on a ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) has to be considered.

Full cardiopulmonary bypass via percutaneous femoral arterial and venous approaches, utilizing a portable cardiopulmonary bypass machine with membrane oxygenator may be used in refractory shock. Recent ECMO data showing high survival to discharge (33–40%) in refractory shock of any cause has been encouraging. VAD support has been used in children with refractory cardiogenic shock from myocarditis, cardiomyopathy and congenital heart disease. More data regarding these modalities are becoming available in children with pediatric septic shock.

PROGNOSIS AND OUTCOME OF SEPTIC SHOCK

Aggressive and early management of shock is associated with intact survival of a child. PALS recommended resuscitation in the emergency resulted in a twofold reduction in mortality and functional morbidity. Similarly, Han et al. found 40% increase in mortality for every hour's delay in resuscitation.

Though the mortality has come down in recent years with implementation of ACCM and PALS guidelines, it may be as high as 30–40% in septic shock requiring multiple inotropes. Similarly, among patients who had multiorgan dysfunction it was 18.6%. Outcome is improved in patients with early normalization of HR (<24 hours), increased CO, elevated oxygen consumption and elevated oxygen extraction, and without significant pulmonary disease. On the other hand, low body temperature (<37°C) pulmonary disease, low cardiac index (<3.3 L/minute/m^2) and decreased oxygen utilization are all poor prognostic indicators in shock. Cardiac function recovers adequately in children treated with vasoactive agents for 24 hours or longer. A fall in procalcitonin after 24 hours of treatment may have favorable prognostic significance. Similarly, there was also a positive correlation of the levels of brain natriuretic peptide (BNP) at 12 hours with severity of illness and myocardial dysfunction.

On long-term follow-up among septic shock survivors, health-related quality of life, anxiety and depression are equal to or slightly better than the age-related controls. Young age at the time of pediatric intensive care admission was predictive of cognitive problems and lower emotional function.

FUTURE DIRECTIONS

Gene expression profiling has been used to discover sepsis-related biomarkers, and thus stratify a patient's immune status and consequently allow for more objective selection of immune-modulating therapies. Advancements in the treatment of septic shock may lie in the ability to tailor therapies according to the specific immune status of an individual patient (stratification).

BIBLIOGRAPHY

1. Angus D, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840-51.
2. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009;32(1):35-9.
3. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375(9730):1969-80.
4. Brierly J, Carcillo J, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009; 37: 666-88.
5. Bronner MB, Knoester H, Sol JJ, et al. An explorative study on quality of life and psychological and cognitive function in pediatric survivors of septic shock. Pediatr Crit Care Med. 2009;10(6):636-42.
6. Carcillo JA, Kuch BA, Han YY, et al. Mortality and functional morbidity after use of PALS/APLS by community physicians. Pediatrics. 2009;124(2):500-8.
7. Costello JM, Cooper DS, Jacobs JP, et al. Intermediate-term outcomes after paediatric cardiac extracorporeal membrane oxygenation–what is known (and unknown). Cardiol Young. 2011;21(Suppl 2):118-23.
8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.

by mansdocs.com

9. Domico M, Liao P, Anas N, et al. Elevation of brain natriuretic peptide levels in children with septic shock. Pediatr Crit Care Med. 2008;9(5):478-83.
10. Feezor RJ, Cheng A, Paddock HN, et al. Functional genomics and gene expression profiling in sepsis: beyond class prediction. Clin Infect Dis. 2005;41(Suppl 7):S427-35.
11. Frazier JW, Hall MW. Immunoparalysis and adverse outcomes from critical illness. Pediatr Clin N Am. 2008;55:647-68.
12. Hatherill M, Tibby SM, Turner C, et al. Procalcitonin and cytokine levels: Relationship to organ failure and mortality in pediatric septic shock. Crit Care Med. 2000;28(7):2591-4.
13. Hobson MJ, Wong HR. Finding new therapies for sepsis: the need for patient stratification and the use of genetic biomarkers. Critical Care. 2011;15:1009.
14. Jaramillo-Bustamante JC, Marı´n-Agudelo A, Ferna´ndez-Laverde M, et al. Epidemiology of sepsis in pediatric intensive care units: first Colombian multicenter study. Pediatr Crit Care Med. 2012;13(5):501-8.
15. Karam O, Tucci M, Ducruet T, et al. Red blood cell transfusion thresholds in pediatric patients with sepsis. Pediatr Crit Care Med. 2011;12:512-8.
16. Koester H, Sol JJ, Ramsodit P, et al. Cardiac function in pediatric septic shock survivors. Arch Pediatr Adolesc Med. 2008;162(12):1164-8.
17. Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. Pediatr Crit Care Med. 2003;4(3):333-6.
18. Long EJ, Shann F, Pearson G, et al. A randomized controlled trial of plasma filtration in severe pediatric sepsis. Crit Care Resusc. 2013;15(3):198-204.
19. Maclaren G, Butt W, Best D, et al. Extracorporeal membrane oxygenation for refractory septic shock in children: one institution's experience. Pediatr Crit Care Med. 2007;8:447-51.
20. Maloney PJ. Sepsis and septic shock. Emerg Med Clin N Am. 2013;31:583-600.
21. Morris MC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. Pediatr Crit Care Med. 2004;5:440-6.
22. Parker MJ, Parshuram CS. Sodium bicarbonate use in shock and cardiac arrest: attitudes of pediatric acute care physicians. Crit Care Med. 2013;41(9):2188-95.
23. Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med. 2012;185:1088-95.
24. Sharma MS, Forbess JM, Guleserian KJ. Ventricular assist device support in children and adolescents with heart failure: the Children's Medical Center of Dallas experience. Artif Organs. 2012;36:635-9.
25. Thiagarajan RR, Laussen PC, Rycus PT, et al. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. Circulation. 2007;116:1693-700.
26. Van der bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ. 2011;342:d3082.
27. World Health Organization. Causes of child mortality for the year 2010. [online]. Available from www.who.int/gho/child_health/mortality/mortality_causes_text/en/index.html. [Accessed January, 2014].
28. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the resolve study. Pediatr Crit Care Med. 2011;12:2-8.

by mansdocs.com

CHAPTER

47

Status Epilepticus

Mullai Baalaaji AR, Sunit Singhi

Status epilepticus (SE) is a life threatening medical emergency with an estimated incidence of 10–27 per 100,000 per year for children from 1 month to 15 years. It necessitates early recognition and urgent treatment as the outcome depends on the rapidity and adequacy of care.

DEFINITION

International League Against Epilepsy defines epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain. SE is defined as a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition. The operational definition of SE is a continuous, generalized convulsive seizure lasting greater than five minutes (in a child older than five years), or two seizures during which the patient does not return to baseline consciousness. For practical purposes, any child who is brought seizing to the emergency room should be treated as stauts epilepticus.

SE is considered refractory (RSE) if seizures persist despite the administration of two appropriate anticonvulsants at appropriate doses, usually a combination of a benzodiazepine and another drug—phenytoin or phenobarbitone. Such an operational definition allows for early recognition of these children so that appropriate treatment can be initiated in a timely manner.

CLASSIFICATION

Status epilepticus (SE) can be classified based on the presence of motor movements.

- Convulsive SE (CSE) consists of continuous clonic or tonic motor activity with bilateral epileptiform discharges on EEG. This progresses to subtle CSE where motor movements are characterized only by twitching of the limbs, face or trunk.
- Nonconvulsive SE (NCSE) consists of continuous electrographic seizures with no motor movements. This also includes absence seizures and focal onset SE without motor manifestations.

ETIOLOGY

The important causes of SE include infections, metabolic causes, hypoxia, toxins, trauma and idiopathic SE. Symptomatic SE implies a known cause which can be either acute symptomatic–infections, toxins or remote symptomatic–associated with a long standing epilepsy or remote central nervous system insult. Idiopathic SE is used when there is no known or suspected cause for the seizures. The important etiologies of SE are listed in Table 1. Table 2 lists the common etiologies encountered in clinical practice.

PATHOPHYSIOLOGY

A failure of physiological neuronal inhibition or an excess of excitation causes the seizures to become sustained. Prolonged seizures have been associated with deficits in γ–aminobutyric acid (GABA) mediated neuronal inhibition because of the rapid internalization of $GABA_A$ receptors. SE causes neuronal injury by both hypoxic-ischemic and excitotoxic mechanisms.

by mansdocs.com

Table 1: Etiology of status epilepticus.

- Infection
  - Sepsis, CNS infections–meningoencephalitis, intracranial abscess.
- Metabolic
  - Hypoglycemia, electrolyte disturbances, renal failure, Hypoxic ischemic encephalopathy, Pyridoxine dependent seizures.
- Drug and Toxins
  - Noncompliance with anti-epileptic medications, drug over dosage, toxins.
- Stroke
  - Ischemic stroke, intracranial hemorrhage, cerebral sinus thrombosis
- Head Trauma
- CNS tumors, Focal cortical dysplasia
- Autoimmune encephalitis
  - Anti-NMDA receptor antibodies, anti-VGKC complex antibodies, paraneoplastic.
- Miscellaneous
  - Hypertensive encephalopathy, Idiopathic epilepsy

Table 3: Complications of status epilepticus.

- *Cardiovascular*: Arrhythmia, cardiac failure or arrest, hypertension, hypotension, shock
- *Respiratory*: Hyperpnea, apnea, irregular or Cheyne stokes breathing, respiratory acidosis, aspiration pneumonia, pulmonary edema
- *CNS*: Raised intracranial pressure, hypoxic-ischemic encephalopathy
- *GIT and Liver*: Acute hepatic failure, bowel ischemia, acute pancreatitis
- *Hematological*: Disseminated intravascular coagulation
- *Renal*: Oliguria, acute renal failure, acute tubular necrosis, myoglobinuria (from rhabdomyolysis)
- *Autonomic*: Hyperpyrexia, excessive sweating, excessive secretions with airway obstruction
- *Metabolic*: Hyperglycemia, hypoglycemia, hyperkalemia, hyponatremia, metabolic acidosis, lactic acidosis

Prolonged seizures cause an increase in neuronal metabolic demand with compensatory increases in cerebral blood flow and brain oxygenation. Later, the homeostatic mechanisms fail and neuronal injury occurs from unmet neuronal metabolic demands. Excitotoxicity by glutamate mediated by N-methyl D-aspartate receptors have been implicated in SE mediated neuronal injury.

During the first 30 minutes of seizures there is sympathetic overactivity, the manifestations of which include tachycardia, hypertension, hyperglycemia and hyperpyrexia. If SE persists for more than one hour, hyperkalemia,

Table 2: Causes of SE in children.

	Number of Patients (%)		
Causes	*Singhi et al. 2005* (n-40)*	*Saz et al. 2011 (n-27)*	*Chin et al. 2006** (n-56)*
• Bacterial/purulent meningitis	12.5	40	9
• Encephalitis	50		
• Idiopathic epilepsy	10	–	10
• Posthypoxic encephalopathy	–	11	1
• Intracranial bleed/stroke	5	8.7	1
• Neurometabolic disorders	5	–	4
• Trauma	–	4.3	2
• Static encephalopathy	–	–	15
• Others†	17.5	45	58

*Refractory status epilepticus

**First episode CSE

†Others include prolonged febrile seizures, neurodegenerative disorders, cortical dysplasia, anti-NMDA receptor antibody, Fever induced refractory epileptic seizures (FIRES), epileptic encephalopathy, brain tumour, neurocutaneous syndromes, congenital malformation and drug induced/withdrawal

hypoglycemia, hypotension and respiratory acidosis may ensue. Massive activation of both sympathetic and parasympathetic systems leads to severe autonomic disturbance including hyperpyrexia, excessive sweating, and salivary and tracheobronchial hypersecretion. CSF pleocytosis may occur. The complications of SE are listed in Table 3.

DIAGNOSIS

Diagnosis depends on the identification of continuous or repetitive seizures, which is straight forward in convulsive SE. However, differentiating nonconvulsive seizures from postictal state can be challenging and requires continuous EEG monitoring for diagnosis.

The following key features help in differentiating common paroxysmal nonepileptic event from true seizure episodes.

- *Vagal Syncope*: Presence of triggers such as prolonged standing, sudden stress, pain, sight of blood. Initial pallor and sweating followed by blurring of vision, dizziness and gradual collapse differentiate it from true seizures.
- *Cyanotic Breath holding spells*: Episode starts with a cry and progresses to apnea and cyanosis. Prolonged episodes may result in syncope, tonic posturing or even reflex anoxic seizures.

by mansdocs.com

- *Jitteriness*: Rapid motor activity such as a tremor, usually induced by a stimulus and can be ended by flexing or holding the limb.
- *Psychogenic*: Child often keeps eyes closed, may respond to suggestion, avoids painful stimuli, limb movements are usually haphazard, and there is rapid return to normal sensorium.

TREATMENT OF STATUS EPILEPTICUS

The principal goal of therapy in SE is to abort the seizures before irreversible neuronal injury occurs.

The objectives of management include:

- Maintenance of adequate airway, breathing and circulation.
- Identify and treat reversible causes—hypoxia, hypoglycemia, dyselectrolytemia.
- Seizure termination and prevention of recurrence.
- Diagnose and initiate treatment of life threatening causes—CNS infections, intracranial space occupying lesions.
- Treatment of raised ICP.
- Manage complications arising from treatment.

INITIAL STABILIZATION

Adequate cerebral oxygenation and perfusion should be achieved by maintaining optimal respiratory and hemodynamic function.

Airway

Patients should be positioned on their side and pharyngeal secretions suctioned out, taking care to minimize the risk of aspiration1p. Oral or nasal airway may be used, but forced opening of clenched jaw should be avoided. Early nasogastric decompression should be done to prevent vomiting and secondary aspiration. If oxygenation is inadequate, early intubation may be required. Endotracheal intubation is also indicated if the child has signs of increased intracranial pressure (ICP) that requires controlled oxygenation and hyperventilation or refractory SE. For successful intubation, rapid sequence intubation (RSI) is the preferred method. In this procedure, after preoxygenation with 100% oxygen and premedication with atropine (0.01–0.02 mg/kg IV) a priming dose of muscle relaxant is given. This is followed by full dose of muscle relaxant and sedation with diazepam in rapid succession.

Breathing

All patients should receive 100% oxygen by mask to ensure adequate oxygenation. Ventilation with bag and mask should be started if there are signs such as inadequate chest movements, poor air entry on auscultation, tachypnea, apnea, poor respiratory effort, central cyanosis, oxygen saturation less than 90%, which indicate inadequate oxygenation and ventilation. If this is found unsatisfactory, the child should be intubated.

Circulation

Circulatory status should be assessed and vascular access should be established immediately for administration of anticonvulsants and fluids. One may use intraosseous access in case of difficult vascular access. Cardiac monitor and transcutaneous oxygen saturation monitor should be applied.

Disability

First line agents used to terminate seizures are benzodiazepines—Lorazepam 0.1 mg/kg IV or Diazepam 0.2–0.3 mg/kg IV, which are repeated after 5 minutes in cases where seizures remain uncontrolled. In situations where vascular access could not be established, rectal Diazepam 0.5 mg/kg or IM, Midazolam 0.2 mg/kg, buccal Midazolam 0.5 mg/kg are alternative agents. A rapid test of blood glucose should be performed and hypoglycemia should be treated with intravenous dextrose.

EVALUATION

Evaluation is done simultaneously to find out the underlying cause. This includes focused history, physical examination and selected investigations (Table 4).

History

The focused brief history should include history of fever, trauma, prior seizures, drug use or withdrawal, underlying medical disorders, perinatal problems, developmental milestones and family history of seizures. If child was already on antiepileptic medications, history regarding missing dose, diarrhea, vomiting, fever, co-medication, under dosage are necessary.

by mansdocs.com

Table 4: Diagnostic workup in status epilepticus.

- *Blood*: Hemogram, Glucose, Calcium, Magnesium, Urea, Electrolytes, ABG, Anti- epileptic drug levels, toxicology screen, Cultures if febrile
- *Urine*: Analysis and toxicology
- *LP (CSF)*: Analysis in suspected meningitis
- *Continuous EEG Monitoring*: In refractory status epilepticus and SE in neonates
- *Neuro Imaging (CT/MRI)*: If focal findings are present or in a case of suspected head injury or coma

Physical Examination

- Sensorium of child (GCS scale), pupillary responses, and motor activity need to be monitored. The presence or absence of meningismus and photophobia should be documented.
- The skin should be examined for petechiae, and signs of neurocutaneous syndromes such as café' au lait spots, ash leaf macules and adenoma sebaceum.
- A thorough neurological examination is performed. In some patients examination may reveal Todd's paresis, a transient paralysis that can follow seizure. It is usually unilateral and may involve both the face and extremities.

TERMINATION OF SEIZURES

Prompt aggressive management of seizures is essential as SE becomes more difficult to control as its duration increases. Most anticonvulsants used to treat SE have the potential to compromise airway and respiratory drive and should be used with necessary precautions.

Step 1

Intravenous Benzodiazepines are considered the first line agents for the initial therapy of SE. Benzodiazepines bind to specific site on $GABA_A$ receptors and enhance inhibitory neurotransmission. Lorazepam (0.1 mg/kg IV given over 2 minutes, maximum 4 mg) or Diazepam (0.3 mg/kg at a rate no greater than 2 mg/minute, maximum 10 mg) or Midazolam (0.1–0.2 mg/kg, maximum 5 mg) can be used as a first line treatment. Lorazepam is favored over Diazepam for initial therapy as it has a longer duration of action and lesser incidence of respiratory depression and hypotension and intubation. However, the need to keep Lorazepam refrigerated and dilute it prior to administration makes Diazepam use easier in acute situations.

Rectal dizepam is considered as effective as IV diazepam; it aborted seizures in 96% of patients in one study, when given within 15 minutes of seizure onset. It is given in a dose of 0.5 mg/kg up to a maximum of 10 mg and may be repeated after 5–10 minutes if seizure persists. It is given without dilution and by using a small syringe or a small catheter on the end of a syringe. It should be infused 4 cms into the rectum. The anal opening should be strapped after administration for about half an hour to prevent leakage of the drug.

Sublingual Lorazepamcan be used in a dose of 0.1 mg/kg up to a maximum of 4 mg and may be repeated after 10 minutes if seizure persists. Rectal lorazepam has not been extensively studied as rectal diazepam. In a study conducted in the pediatric population comparing rectal and intravenous diazepam and lorazepam, there were minimal differences in the meantime to seizure control for both the drugs with both types of administration.

Intramuscular (IM) Midazolam: Midazolam is water soluble and can be administered IM. IM midazolam has been used as first line drug for controlling SE and a dose of 0.2 mg/kg is reported to be clinically efficacious in more than 90% of children in SE. It is particularly valuable when there is difficulty in establishing an intravenous route.

Buccal midazolam was shown to be as effective as rectal diazepam if not more, in a randomized study conducted in children and young people with SE lasting for more than 5 minutes. Intranasal midazolam administration is safe, inexpensive and can be used by parents and paramedical people for acute seizures.

Correctable metabolic causes of status epilepticus like hypoglycemia, hypocalcemia, hyper/hyponatremia and hypomagnesemia must be identified and treated. First dose of empirical intravenous antibiotics (ceftriaxone @ 100 mg/kg/day or cefotaxime @ 200 mg/kg/day) must be administered in cases of suspected meningitis. Empirical intravenous acyclovir (@ 20 mg/kg/dose every 8 hourly) must be started in children suspected to have acute meningoencephalitis.

Step 2

Phenytoin inhibits voltage gated sodium channels and blocks repetitive neuronal firing. It is given intravenously in a loading dose of 20 mg/kg as infusion diluted in normal saline at a rate no more than 1 mg/kg/min. A supplemental bolus of 10 mg/kg can be repeated if the seizures persist. Phenytoin must be infused slowly to minimize the risk of cardiac arrhythmias, infusion site

by mansdocs.com

pain and thrombophlebitis. Extravasation at infusion site has been associated with localized extremity edema and discoloration—"purple glove syndrome". If seizures do not recur, maintenance dose of phenytoin (5–8 mg/kg/day) should be given after 12–24 hours of the initial loading dose Fosphenytoin, a water soluble phenytoin prodrug can be administered IM with rapid and complete absorption. The dose of fosphenytoin is 15–20 mg/kg of Phenytoin equivalents/kg, infused at a rate of not more than 3 mg/kg/min, not to exceed 150 mg/min. Fosphenytoin is preferred because it is better tolerated at the infusion site, has a lower risk for arrhythmias and hypotension and not been associated with the purple glove syndrome. However the cost precludes its widespread use.

Step 3

Phenobarbitone acts through $GABA_A$ receptor and increases chloride mediated conductance. It is preferred to phenytoin in neonates if there was no initial response to benzodiazepines. It is given in a loading dose of 15–20 mg/kg IV at a rate of 1.5 mg/kg/min. In neonates an additional dose of 5–10 mg/kg may be given. The maintenance dose is 3–5 mg/kg/day given in two divided doses, 12–24 hours later. Owing to the cumulative respiratory depressant effect of benzodiazepines and barbiturates, facilities should be available for mechanical ventilation.

SE not controlled with above line of management is considered refractory SE.

Intravenous Valproate: Use of intravenous valproate has shown promising result in the management of refractory status epilepticus. Sodium valproate acts through modulation of sodium and calcium currents as well as through $GABA_A$ receptor. Respiratory depression and hypotension are less common in valproate compared to diazepam. Hepatotoxicity is a concern in children with metabolic disorders which is a concern in children with RSE.

Preliminary studies in adults and in children have shown that sodium valproate is effective and safe over a large range of doses as well as various rates of administration, including when given as a rapid bolus. Intravenous sodium valproate is as effective as diazepam infusion is controlling refractory status epilepticus in children and it is free of adverse effects such as respiratory depression and hypotension. Sodium valproate is given as an initial loading bolus of 30 mg/kg diluted 1:1 in normal saline over 2–5 min. If the status is not controlled within 10 minutes after the bolus dose, a repeat bolus dose of 10 mg/kg is given, followed by infusion at rate of 5 mg/kg/hr, which is continued until a seizure free period of 6 hours and then reduced at a rate of 1 mg/kg/hr every 2 hourly. After discontinuation of intravenous infusion, a maintenance dose of 10 mg/kg/dose 8 hourly IV is continued until the child could take oral anticonvulsants.

Intravenous Levetiracetam

Intravenous Levetiracetam is a recent addition to the drugs used for SE and in a recent observational study, seizure control was achieved in 59% of children with repeated seizures and 83% of children with SE. The median dose was 14.4 mg/kg (range 5–30 mg/kg) and there were no major acute side effects noted, thus having a promising safety and tolerability.

Step 4

If seizure activity persists after the above mentioned treatment, the child should be put on a ventilator and continuous EEG monitoring and benzodiazepine infusion or anesthetic agents are used. It is recommended to escalate treatment to achieve burst suppression pattern on EEG which is maintained for atleast 12 hours before a medication taper is attempted. If seizures recur when medication is tapered, then therapy is reinstated to achieve burst suppression for another 48 hours.

Benzodiazepine Infusion

Diazepam or midazolam infusion can be considered if there was an initial response to benzodiazepines. Diazepam is diluted in normal saline, Ringer's lactate or dextrose to give strength of 0.04 mg/mL and started at a dose of 0.01 mg/kg/min. Most children require 0.02–0.03 mg/kg/min. Midazolam infusion starting with 2 µg/kg/min up to 12 µg/kg/min may be used. In a study in the author's unit, both of these drugs controlled RSE on an average within 15 minutes, however midazolam group had higher seizure recurrence (57% vs 16% in diazepam group) and higher mortality (38% vs 10.5% in diazepam).

Barbiturates

Thiopental is administered as loading dose of 3–4 mg/kg over 2 minutes, followed by a continuous infusion of 2 mg/kg/min and increased every 3–5 minutes by 0.1 mg/kg/min. Barbiturate coma achieved seizure control in 74–100% of patients, however its use is limited by side

by mansdocs.com

effects–respiratory depression, hypotension requiring vasopressors support, immunosuppression. During treatment with barbiturates, Midazolam and phenobarbitone are discontinued, while phenytoin should be maintained at therapeutic levels.

Propofol

Propofol is comparable to thiopentone for seizure control, however prolonged use is not recommended in children due to reports of fatal propofol infusion syndrome. The initial dose is 1–3 mg/kg followed by continuous infusion of 2–10 mg/kg/hr.

Ketamine

Ketamine is an NMDA antagonist which has neuroprotective role in experimental models, and is found to be effective in RSE.

Lidocaine

The initial dose is 1–2 mg/kg IV given over 2 minutes, and continuous infusion is initiated at 2–4 mg/kg/hr. Side effects include hypotension, heart block, arrhythmia, and seizures at higher doses.

Inhalational Anesthetics

Isoflurane has been used to treat RSE but have not been subjected to clinical trials.

In an unpublished study from the author's unit, Sodium valproate, Phenobarbitone, Levetiracetam were commonly employed as third line agents in 62%, 30% and 22% of patients with RSE. Midazolam infusion, Diazepam infusion, Thiopentone coma was needed in 18%, 9% and 7% of children respectively.

Table 5 lists the stepwise escalation of treatment in managing SE.

Other Treatment Options

Pyridoxine Infusion

Intravenous pyridoxine is effective in treatment of rare patients with an inborn error of metabolism of pyridoxine. It has also been claimed to be effective in non-pyridoxine dependent patients. The doses used ranged from 180–600 mg/day.

Immunotherapy

Immune modulating therapies include steroids, adrenocorticotropic hormone, intravenous immunoglobulins and plasma exchange. Plasmapheresis may result in the reduction of drug levels, especially those antiepileptic drugs that are not highly protein bound, and a reduction in immunoglobulin G levels requiring careful therapeutic drug monitoring with supplemental antiepileptic drug doses given after plasmapheresis. Anti-N-methyl-D-aspartate receptor–associated encephalitis, Hashimoto's encephalitis, Rasmussen encephalitis are a few conditions which respond to immune-modulation therapies.

Resective Neurosurgery

Various modalities available are focal resection, multiple subpial transection, corpus callosectomy and hemispherectomy.

Ketogenic Diet

Ketogenic diet has been used in encephalopathic epilepsies of early childhood and its use in RSE is limited to case reports. Before initiation of ketogenic diet, metabolic disorders need to be screened which would be exacerbated by ketogenic diet.

Other Options

Vagal nerve stimulation, deep brain stimulation, Electroconvulsive therapy, CSF drainage have been reported to be useful in RSE in case reports.

OUTCOME

The mortality ranges from 3–5% in children[2] and the mortality rates for cases with unprovoked or febrile CSE are much lower (0.2%) than those associated with acute symptomatic CSE (12.5–16%). Neurological sequelae including secondary epilepsy, cognitive deterioration, behavioral problems and focal neurologic deficits are reported in upto 15% of children. The most important determining factor for prognosis and outcome in both CSE and NCSE is the underlying cause. Additionally, patient age and duration of SE are also contributing factors. When there is non-idiopathic, nonfebrile etiology and no acute or progressive CNS insult, morbidity and mortality are low. On the other hand mortality and morbidity are highest with SE associated with CNS infections. Better prognosis and outcome in the future will depend on improvements ensuring early diagnosis of any underlying disorders and their appropriate subsequent treatment.

by mansdocs.com

Table 5: Stepwise management of SE.

	Drug	*Supportive treatment*
0–3 minutes	Initial stabilization and supporting vital functions as mentioned above	
3–5 minutes	*Benzodiazepine first line therapy* *Lorazepam*:* 0.1 mg/kg over 2 minutes (max 4 mg)	Start second IV line for simultaneous administration of second medication and IV fluids
	OR	
	Diazepam: 0.3 mg/kg over 2 minutes (max 10 mg) Correct hypoglycemia, hypocalcemia, hyper/hyponatremia, hypomagnesemia.	
7–8 minutes	*Phenytoin*:** 20 mg/kg dilute in saline and infuse at a rate of not more than 1 mg/kg/min	Thiamine 100 mg iv push; Pyridoxine 100 mg iv push in children < 3 years of age
10 minutes	*Repeat Diazepam*: 0.3 mg/kg OR *Lorazepam*: 0.1 mg/kg	
15 minutes	*Repeat Diazepam*: (same dose) OR *Lorazepam*: 0.1 mg/kg	
25 minutes	*Phenytoin*: 10 mg/kg dilute in saline and infuse at a rate not more than 1 mg/kg/min	
35 minutes	*IV Valproate 30 mg/kg diluted 1*: 1 in normal saline over 2–5 minutes. If the status is not controlled within 10 minutes of bolus, repeat 10 mg/kg bolus dose, followed by continuous infusion at the rate of 5 mg/kg/hr (18)***	Transfer to PICU, prepare for intubation, ventilation, get EEG
	OR	
	Midazolam OR Diazepam infusion(19)# *Diazepam*: 0.01 mg/kg/min, max 0.1 mg/kg/min *Midazolam*: 2 mcg/kg/min up to 12 mcg/kg/min in increments of 2 mcg/kg/min every 5 minutes	Cardiorespiratory monitoring
	Levetiracetam: 40 mg/kg at 5 mg/kg/minute can be infused after valproate before initiating thiopental coma	
45–50 minutes	*Thiopental*:## 3–4 mg/kg iv over 2 minutes followed by an infusion at 2 mg/kg/hr.	Mechanical ventilation

*Lorazepam must be refrigerated and diluted before administration

**If the patient is already on Phenytoin, then administer 8 mg/kg of as the initial anticonvulsant

***If the patient is already on Valproate, then 10 mg/kg is the loading dose. The infusion is continued until seizure free period of 6 hours, then tapered off @ of 1 mg/kg/hr every 2 hourly.

#Midazolam or Diazepam infusion is preferred over Valproate in children less than 2 years. Benzodiazepine infusion is discontinued once thiopental infusion is started

##Infused in a separate IV line to avoid mixing with acidic drugs. Increase the infusion @ 1 mg/kg/hr every 30 minutes to 6 mg/kg/hr till seizure control and burst suppression on EEG, The infusion is continued until seizure free period of 6 hours, then tapered off.

BIBLIOGRAPHY

1. Alexopoulos A, Lachhwani DK, Gupta A, et al. Resective surgery to treat refractory status epilepticus in children with focal epileptogenesis. Neurology 2005;64:567–70.
2. Andrews PI, Dichter MA, Berkovic SF, et al. Plasmapheresis in Rasmussen's encephalitis. Neurology 1996;46:242-6.
3. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368:222-9.
4. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.
5. Govoni V, Fallica E, Monetti VC, et al. Incidence of status epilepticus in southern Europe: A population study in the health district of Ferrara, Italy. Eur Neurol 2008;59:120-6.
6. Holmes GL, Riviello JJ Jr: Midazolam and pentobarbital for refractory status epilepticus. Pediatr Neurol. 1999;20: 259-64.
7. Kim SJ, Lee DY, Kim JS: Neurologic outcomes of pediatric epileptic patients with pentobarbital coma. Pediatr Neurol. 2001;25:217-20.
8. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of sttusepilepticus. Epilepsia 1999;40:120-2.
9. Major P, Thiele EA. Seizures in children. Determinig the variation. Pediatr Rev, 2007;28:363-71.

by mansdocs.com

10. McTaque A, Kneen R, Kumar R, et al. Intravenous levetiracetam in acute repetitive seizures and status epilepticus in children: experience from a children's hospital. Seizure 2012 Sep;21(7):529-34.
11. Nabbout R, Mazzuca M, Hubert P, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). Epilepsia 2010;51: 2033–7.
12. Obeid M, Mikati M. Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy. PediatrNeurol 2007;37(5):309-16.
13. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and Epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) Epilepsia 2005;46(4): 470-2.
14. Rosati A, L Erario M, Ilvento L, et al. Efficacy and safety of ketamine in refractory status epilepticus in children. Neurolgy 2012;79(24):2355-8.
15. Rossetti AO, Milligan TA, Vulliemoz S, et al. A randomized trial for the treatment of refractory status epilepticus. Neurocrit care 2011;14:4-10.
16. Singhi S, Murthy A, Singhi P, et al. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol. 2002;17(2):106-10.
17. Thakker A, Shanbaq P. A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. J Neurol. 2013;260(2):470-4.
18. Vezzani A, Ruegg S. Immunity and inflammation in epilepsy: a mechanistic insights and therapeutic perspectives. Epilepsia 2011; 52 (Suppl 3):1–53.
19. Wilfong A. Differential diagnosis of seizures in children. In: Rose BD, editors. UpToDate. Waltham MA, 2007.

by mansdocs.com

CHAPTER 48

Raised Intracranial Pressure in Children with an Acute Brain Injury: Monitoring and Management

R Ramesh Kumar, Sunit Singhi

INTRODUCTION

Children with acute brain injury due to various neurologic and non-neurological illnesses commonly develop raised intracranial pressure (ICP). Almost 93% of children with acute meningitis have signs of raised ICP at admission or develop these within 48–72 hours of admission. It is a medical emergency requiring prompt diagnosis, monitoring and goal-directed management otherwise it may cause secondary brain injury due to reduced cerebral perfusion pressure (CPP), and progress into herniation syndrome and death. Appropriate and timely management of raised ICP is possible with proper understanding of pathophysiology, and various therapeutic modalities.

The aim of clinicians treating a child with raised ICP is to break the vicious cycle of cerebral edema and compromised cerebral blood flow (CBF) at the earliest and to maintain adequate CPP. Because of potential side effects of therapy and intensive ICP monitoring, identifying patients at risk of developing raised ICP is crucial in preventing pathologic changes that may result in poor outcome and increased mortality. The creation of standardized management protocol has reduced variations in ICP, decreased duration of raised ICP and improved outcome.

CEREBRAL PHYSIOLOGY AND INTRACRANIAL DYNAMICS

Monro-Kellie Doctrine

It is crucial to understand the Monro-Kellie doctrine because management of increased ICP revolves around this basic principle. Monro-Kellie doctrine states that in a noncompliant skull vault, ICP is the sum total of pressure exerted by the brain (≈80%), blood (≈10%) and cerebrospinal fluid (CSF) (≈10%). When there is an increase in any one of these components, one or more of the other components must decrease to keep the total volume the same or else the ICP will increase. The blood and the CSF are the only compartments that can compensate. In response to increase in intracranial volume, initial compensation occurs by displacement of CSF from the ventricles and the cerebral subarachnoid space to spinal subarachnoid space (vertebral canal), decreased production and increased absorption of CSF. But when these adaptations have been exhausted, an inflection point is reached beyond which ICP increases exponentially. Infants (usually less than 18 months) and children with open fontanels and sutures may be able to compensate better but will still be susceptible to acute increases in ICP.

Intracranial Pressure: Normal Values

The normal range for ICP varies with age. Values for children are not as well established as for adults. The usual normal range is considered as 5–15 mm Hg. ICP can be subatmospheric in newborns. In newborn term infants it is 1.5–6 mm Hg, in young children 3–7 mm Hg and in older children 10–15 mm Hg.

Intracranial Pressure: Threshold for Treatment

Raised ICP is a clinical condition defined as the persistent elevation of ICP above 20 mm Hg for more than 5 minutes

by mansdocs.com

in a patient who is not being stimulated. There is a general consensus that an ICP more than 20 mm Hg should be treated. There is some rationale for treating smaller elevations (>15 mm Hg) to avoid larger elevations that can cause cerebral herniation and irreversible brainstem injury. For all practical purposes, if symptoms and signs of raised ICP are present, one should consider that ICP is more than 20 mm Hg and treat accordingly. Sustained ICP values greater than 40 mm Hg indicate severe, life-threatening intracranial hypertension. There have been some suggestions that lower threshold values for younger children may be used, although there are no data to support this. A surge in ICP normally occurs with activities such as suctioning, painful stimuli and coughing, and does not warrant intervention if it does not return to baseline within 5 minutes. It is important to distinguish "normal" or expected increases in ICP versus intracranial hypertension because the latter requires prompt intervention.

Compliance and Autoregulation

Compliance is an indicator of the brain's tolerance to variations (increase) in ICP. Each patient has varying degrees of compliance even with similar injuries. When the patient's compliance is exhausted, there is a dramatic increase in the pressure/volume curve leading to a rapid elevation in ICP. *Autoregulation* is the maintenance of a steady CBF by vasoconstriction and vasodilatation of the cerebral vessels despite fluctuations in systemic blood pressure (BP) (50–150 mm Hg). If autoregulation is impaired, CBF and cerebral blood volume (CBV) will be dependent on changes in systemic BP. The main physiologic influences on CBF are the partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygenation, pH, CPP and cerebral metabolic rate. An increase in $PaCO_2$, acidosis and hypoxemia will increase CBF by causing vasodilatation, which will increase CBF, and thereby potentially increase ICP. CBF in excess of tissue demand will lead to hyperemia. CBF of healthy children was found to be as high as 108 mL/100 g/min. CBF less than 20 mL/100 g/min is usually indicative of cerebral ischemia and has been associated with a poor outcome in children with traumatic brain injury (TBI).

Cerebral Perfusion Pressure

Cerebral perfusion pressure is the pressure at which brain is perfused. It provides an indirect measure of adequacy of CBF. It is calculated as the difference between mean arterial blood pressure (MABP) and ICP (CPP = MABP – ICP), where MABP = one-third systolic pressure plus two-third diastolic pressure. Normal CPP values for children are not clearly established, but the values that are generally accepted as the minimal CPP necessary to prevent ischemia are as follows: infants/toddlers greater than 40–50 mm Hg; children greater than 50–60 mm Hg. CPP less than 40 mm Hg is a significant predictor of mortality in children with TBI. Autoregulation is likely to get lost at CPP values less than 50 mm Hg. Ability to autoregulate pressure may be impaired or lost even with a normal CPP; CBF can passively follow changes in CPP.

PATHOPHYSIOLOGY RELATED TO RAISED INTRACRANIAL PRESSURE

Based on the Monro-Kellie doctrine, an increase in ICP is commonly caused by an increase in volume of brain (cerebral edema), blood (intracranial bleeding), space occupying lesion or CSF (hydrocephalus). These mechanisms could be operative independently or in various combinations. Cerebral edema is the most important cause of raised ICP in nontraumatic brain injuries such as central nervous system (CNS) infections, and systemic and metabolic encephalopathies. Cerebral edema can be categorized as vasogenic, cytotoxic or interstitial. However, rarely one does occur in isolation; rather, a patient with cerebral edema may have a combination of all three mechanisms. Vasogenic cerebral edema is due to injury to blood-brain barrier and increased capillary permeability around the area of injury or inflammation particularly in CNS infections. It can be local or diffuse, and occurs around mass lesions and inflammatory processes (e.g. meningitis, encephalitis). Interstitial cerebral edema is due to an increase in the hydrostatic pressure of CSF and is often observed in patients with obstructive hydrocephalus or excessive CSF production. Cytotoxic cerebral edema (cellular swelling) occurs following cerebral ischemia and hypoxia, causing irreversible cell damage and death. Osmolar swelling may occur due to increased local osmolar load around necrotic foci caused by infarction or contusion, and possibly because of increased CBV (hyperemia) in CNS infections.

ETIOLOGY OF RAISED INTRACRANIAL PRESSURE

Common causes of raised ICP with respect to pathophysiology are shown in Box 1.

by mansdocs.com

Box 1: Common causes of raised intracranial pressure.

- *Increase in brain volume*
  - *Cerebral edema*: Primary CNS illness—encephalitis, meningitis, head injury, Reye's syndrome
    Cerebral edema: Secondary to systemic illness—hypoxic ischemic injury (hypoventilation, shock), ischemic stroke/infarct, metabolic encephalopathy (hyperpyrexia), hepatic failure, lead intoxication
  - *Space-occupying lesions*: Hematomas, tumors, abscesses
- *Increase in blood volume*
  - *Venous obstruction*: Cerebral venous sinus thrombosis
  - Hemorrhage
  - *Vasodilatation*: Due to hypoxia, drugs or hypercapnia
  - Status epilepticus
- *Increase in CSF volume*
  - Obstructive hydrocephalus, communicating hydrocephalus
  - *Impaired reabsorption*: Subarachnoid hemorrhage
  - *Increased production*: Tumors
- *Idiopathic or benign intracranial hypertension*

(CNS: Central nervous system; CSF: Cerebrospinal fluid).

The primary etiology could be intracranial or extracranial. When primary cause of increased ICP is intracranial, normalization of ICP depends on rapidly addressing the underlying brain disorder. Intracranial hypertension due to an extracranial or systemic process is often remediable. Increased ICP can also occur after a neurosurgical procedure. Following TBI, intracranial hypertension is multifactorial:

- Trauma induced epidural or subdural hematomas, hemorrhagic contusions and depressed skull fractures
- Cerebral edema (most important cause after hematomas)
- Hyperemia due to loss of autoregulation
- Hypoventilation leading to hypercarbia and consequently cerebral vasodilation
- Hydrocephalus resulting from obstruction of the CSF pathways or its absorption
- Increased intrathoracic or intra-abdominal pressure as a result of mechanical ventilation, posturing, agitation or Valsalva maneuver.

A secondary increase in the ICP is often observed 3–10 days after the trauma, mainly as a result of a delayed formation of epidural or acute subdural hematoma or traumatic hemorrhagic contusions with surrounding edema, sometimes requiring evacuation. Other potential causes of delayed increases in ICP are cerebral vasospasm, hypoventilation and hyponatremia.

ASSESSMENT AND MONITORING

The initial assessment of the neurologically injured child consists of assessment of ABCs (airway, breathing and circulation), Glasgow Coma Scale (GCS) score, cranial nerve function, signs and symptoms of increased ICP, temperature and cardiorespiratory assessment. Astute observation of any abnormal respiratory patterns is crucial; since this may be the first vital sign change indicating neurological dysfunction. The most ominous cardiorespiratory abnormality is Cushing's triad. Cushing's triad occurs when there is cerebral ischemia causing peripheral vasoconstriction. This vasoconstriction leads to an increase in systolic BP to improve cerebral perfusion. Cardiac baroreceptors sense this increased BP, resulting in a vagal response manifested as bradycardia. Abnormal or irregular respirations are the final component of Cushing's triad and occur due to brainstem. All patients with a modified GCS (m-GCS) less than or equal to eight are the likely candidates for raised ICP, and in particular the patients with following diagnosis:

- Acute CNS infection with change in mentation/focal signs
- *Traumatic brain injury*: Severe TBI (m-GCS ≤ 8), mild to moderate TBI with abnormal admission head computed tomography (CT) scan or hypotension, motor posturing
- Acute hepatic encephalopathy grade III or IV
- Diabetic ketoacidosis with encephalopathy
- Toxic encephalopathy, hypertensive encephalopathy
- Hypoxemic encephalopathy—gross ischemia greater than 50% middle cerebral artery (MCA) territory infarction.

Urgent neuroimaging may be needed, after stabilization of ABC and reversing potential or clinically manifest herniation, to rule out surgically correctable causes of raised ICP.

CLINICAL SIGNS

Clinical symptoms and signs of raised ICP are highly variable and depend on the nature of the primary brain insult, the extent of compartmentalization, the presence and location of a mass lesion, and the rate of increase in ICP. Clinical symptoms of increased ICP, such as headache, nausea and vomiting, are impossible to elicit in comatose patients.

In conscious patients, irritability, headache, vomiting, confusion and decreased alertness, and neck retraction

by mansdocs.com

may be the presenting features. These are neither sufficiently sensitive nor specific for timely recognition of raised ICP. Tense fontanel on palpation and papilledema are reliable signs of raised ICP, but the later usually absent in acute conditions, even in patients with documented elevated ICP.

In unconscious/comatose patients, raised ICP should be suspected in all patients with head injury, meningitis, encephalitis, liver disease and diabetes mellitus. The clinical features strongly favoring raised ICP are generally seen late, when brain herniation is imminent or has already set in. These are abnormal posturing (decerebration or decortication), abnormal pupillary dilatation, hypertension, bradycardia, irregular breathing, sixth nerve palsy and papilledema.

Cushing reflex becomes evident only later in the course of illness and may not occur in young children. Abnormal pupillary dilatation and posturing can occur in the absence of raised ICP. CT scan signs of brain swelling are predictive of increased ICP, but the CT scan may be normal even in the presence of documented raised ICP.

Signs of Brain Herniation Syndrome

Pressure gradient between various intracranial compartments may lead to herniation of brain from one compartment to another. Early signs of herniation are mainly due to compression and ischemia rather than displacement of brain tissue. Prompt recognition of the clinical signs of herniation is critical to salvage life. Mechanisms, clinical manifestation and imaging finding are given in Table 1.

INTRACRANIAL PRESSURE MONITORING

Acute raised ICP is an important cause of secondary brain injury hence at-risk patients should have close monitoring of systemic parameters including temperature, heart rate, BP, electrocardiogram, blood glucose, ventilation, oxygenation, and fluid intake and output. They should be on continuous monitoring with pulse oximetry and capnography to avoid unrecognized hypoxemia and hypoventilation or hyperventilation. A central venous catheter

Table 1: Herniation syndromes.

Syndrome	*Mechanism*	*Clinical finding*	*Imaging finding*
Transtentorial—descending unilateral (uncal)	• Medial temporal lobe pushes downward into the posterior fossa through the incisura	• *Ipsilateral pupil dilation*: Earliest sign • External ophthalmoplegia • Contralateral hemiparesis • Decerebrate posturing • Impairment in consciousness	• Contralateral temporal horn and ipsilateral ambient cistern widening • Ipsilateral prepontine cistern widening • Uncus extending into the suprasellar cistern
Transtentorial—descending bilateral (central)	• Downward displacement of the cerebral hemispheres and the basal nuclei compressing and displacing the diencephalon and the midbrain rostrocaudally through the tentorial notch	• Medium-sized, fixed pupils • Early coma • Decorticate posturing • Cheyne-Stokes respiration • Diabetes insipidus	• Effacement of sulci • Obliteration of the suprasellar cistern • Compression and posterior displacement of the quadrigeminal cistern
Transtentorial—ascending	• Infratentorial mass effect protruding upward compressing the midbrain	• Nausea/vomiting • Progressive stupor	• Spinning top appearance of midbrain • Narrowing of bilateral ambient cisterns • Filling of quadrigeminal cisterns
Subfalcine—cingulate	• Brain tissue extending under the falx in the supratentorial cerebrum	• Small reactive pupils • Headache • Contralateral leg paralysis	• Attenuation of ipsilateral aspect of frontal horn • Asymmetric anterior falx • Obliteration of ipsilateral atrium of lateral ventricle • Septum pellucidum shift
Tonsillar	• Cerebellar tonsils protruding below the foramen magnum compressing the medulla and upper cervical cord	• Hypertension, bradycardia, bradypnea • Coma • Respiratory arrest • Bilateral arm dysesthesia	• Cerebellar tonsils at the level of the dens on axial images • Cerebellar tonsils on sagittal images 5 mm below foramen magnum (7 mm in children)

by mansdocs.com

should be placed to evaluate volume status and a Foley catheter for accurate urine output. Patients with suspected intracranial hypertension should have monitoring of ICP. Monitoring of cerebral oxygen (O_2) extraction with jugular bulb oximetry is desirable, if available.

Indications

Intracranial pressure monitoring is advocated for patients at high risk for raised ICP, especially for those with a worsening examination due to the poor reliability of clinical signs and symptoms of raised ICP and the need for prompt recognition and timely intervention. Although no randomized trial has been done in children, retrospective studies and reviews on aggressive management of raised ICP with ICP monitoring have shown improved outcome in TBI, intracranial hemorrhage (ICH) and acute CNS infections. It is not the monitor itself that improves outcome, but the information gleaned from this modality that guides appropriate interventions.

For a favorable risk-to-benefit ratio, ICP monitoring is indicated only in selected at-risk patients. These include patients with GCS of 8 or less and patients with TBI who have an abnormal admission head CT scan. Other less common indications include patients with multiple systemic injuries with altered level of consciousness and subsequent to removal of an intracranial mass (e.g. hematoma, tumor). ICP monitoring also must be considered in nontraumatic conditions in which an intracranial mass lesion is present (e.g. cerebral infarction) and has a likelihood of expansion leading to intracranial hypertension and clinical deterioration.

The duration of monitoring is until ICP has been normal for 24–48 hours without the need for therapy to reduce ICP. ICP monitoring makes raised ICP management straightforward with clear goals of therapy, enabling early identification of refractory cases for more aggressive interventions to prevent cerebral herniation and preserve cerebral perfusion. It is also necessary to monitor ICP in order to calculate the CPP.

Sites for Intracranial Pressure Monitoring

There are four main types of ICP monitors used in standard ICU practice: intraventricular catheter, intraparenchymal pressure transducer, subarachnoid bolts and epidural transducers. The most common sites used are intraventricular and intraparenchymal. Intraventricular catheter remained the preferred device for monitoring ICP and the standard against which all latest monitors are compared. These days, the use of intraventricular catheter placement, preferably with an implantable microtransducer (fiber optics or strain gauge), allows simultaneous monitoring of ICP and management of increased ICP by CSF drainage. The advantages of the ventriculostomy are its relatively low cost, the option to use it for therapeutic CSF drainage and its ability to recalibrate to minimize errors owing to measurement drift. Disadvantages are difficulties with insertion into compressed or displaced ventricles, risk of infection, inaccuracies of the pressure measurements because of obstruction of the fluid column and the need to maintain the transducer at a fixed reference point relative to the patient's head. The system should be checked for proper functioning at least every 2–4 hours, and any time there is a change in the ICP, neurologic examination (Flowchart 1) and CSF output. This check should include assessment for the presence of an adequate waveform which should have respiratory variations and transmitted pulse pressure.

Fiber-optic intraparenchymal pressure transducer uses a catheter tip in solid state, which senses changes in the amount of light reflected off a pressure sensitive diaphragm located at the tip of fiber-optic catheter. Advantages of this monitoring are its ease of placement and it allows direct measurement of brain tissue pressure in patients with compressed or dislocated ventricles in which placement of intraventricular catheters would be difficult. A solid-state system does not have the pitfalls of the fluid-filled system. Also, it is not easily occluded by air bubble and debris. Disadvantages include mechanical failure and inability to recalibrate these devices in situ, if there is drift of dampening of waveforms. Differences between simultaneously recorded intraventricular pressures and those from intraparenchymally placed fiber-optic devices have been reported and show that they as effective in recording of waveform signals and values.

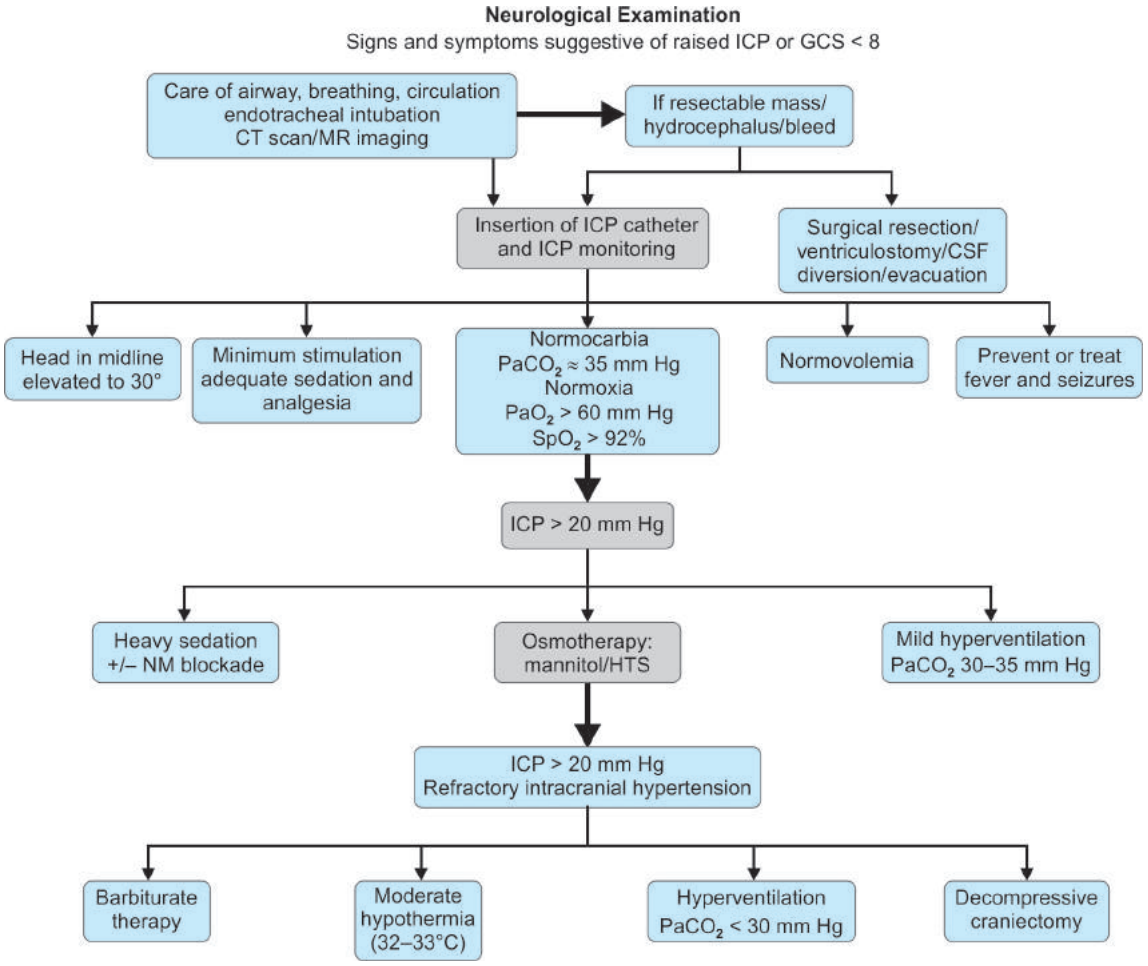
Intracranial Pressure Waveforms

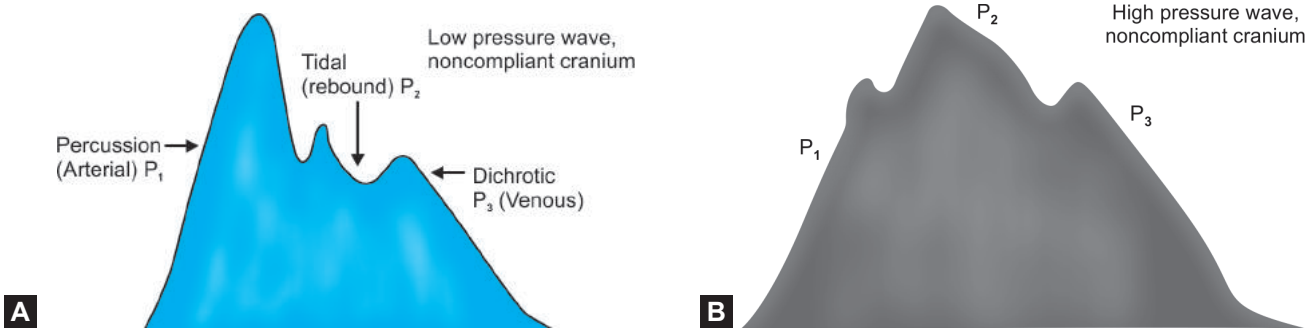
The normal ICP waveform contains three phases (Fig. 1A):

1. P_1 (percussion wave) represents arterial pulsations
2. P_2 (tidal wave) reflects intracranial compliance
3. P_3 (dicrotic wave) represents venous pulsations.

by mansdocs.com

Flowchart 1: Raised intracranial pressure algorithm. Continual assessment of neurological and cardiorespiratory status is imperative.





Figs 1A and B: (A) Normal intracranial pressure waveforms; (B) High intracranial pressure waveforms.

As the ICP increases, cerebral compliance decreases, arterial pulses become more pronounced and venous components disappear. Pathologic waveforms include Lundberg A, B and C types (Fig. 1B). Lundberg A waves or plateau waves are ICP elevations to more than 50 mm Hg lasting 5–20 minutes. These waves are accompanied by a simultaneous increase in mean arterial pressure (MAP), but it is not clearly understood if the change in MAP is a cause or effect. Lundberg B waves or pressure pulses have amplitude of 50 mm Hg and occur every 30 seconds to 2 minutes. Lundberg C waves have amplitude of 20 mm Hg and more and a frequency of 4-8/min; they are

by mansdocs.com

seen in the normal ICP waveform, but high amplitude C waves may be superimposed on plateau waves.

Complications of Intracranial Pressure Monitoring

Certain investigators raised concerns regarding the possibility of infection, potential brain damage and hemorrhage as complications of ICP monitoring. The most common complication of ventricular catheter placement is infection (incidence of 5–14%); colonization of the device is more common than clinical infection. There was a nonlinear increase of risk during 10–12 days, after which the risk diminished. Use of antibiotic-coated ventricular catheters has been shown to reduce the risk of infection from 9.4% to 1.3%. Other complications of ventricular catheters are hemorrhage (incidence 1.4%), malfunction, obstruction and malposition.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

In patients with raised ICP, in addition to treatment of primary cause, the main focus of treatment is to prevent and minimize secondary brain injury. Secondary brain injury refers to the processes that occur within hours to days after the primary injury that can be prevented or minimized, such as cerebral ischemia, cerebral edema and neurochemical alterations, including excitatory neurotransmitters, the formation of free radicals, and increased levels of intracellular calcium and potassium. The neurological devastation caused by the secondary injury is often worse than the underlying primary disorder. The management of raised ICP primarily revolves around reduction in volume of one of the three intracranial compartments: brain, blood and CSF. Treatment response is highly dependent on multiple factors including the nature of primary brain injury, the extent of tissue shift, cerebral edema, mass effect, obstruction of CSF flow and the status of the cerebrovascular autoregulatory reserve.

Most of the current treatment recommendations are based on consensus and clinical experience. A few specific treatment options have been subjected to randomized trials. Since there are limited outcome studies to support the current management of children with increased ICP from etiologies other than TBI, it is the knowledge gained from treating TBI that is often applied to treat raised ICP of other etiologies also.

GOALS AND PRINCIPLES OF THERAPY

The immediate goal is to prevent progression to herniation or to reverse the herniation, if present; and then to maintain a CPP greater than 60 mm Hg and ICP less than 20 mm Hg. The principles of management include maintaining normoxia and normocarbia; avoiding factors that aggravate or precipitate raised ICP, namely fever, hypoxia, hypoglycemia, hypotension and any noxious stimulation; treatment of underlying cause including surgical intervention; maintain adequate MABP (more than fiftieth percentile for given age and gender) with help of fluid and, if needed, vasoactive therapy; and bringing down ICP.

Therapeutic measures to bring down ICP, after surgical management of mass lesions, are divided into first-tier and second-tier therapies (Box 2). First-tier therapies include elevation and positioning of head, sedation and analgesia,

Box 2: Therapeutic modalities to reduce raised intracranial pressure.

- *General measures and first-tier therapy*
  - Head in neutral position, 30° elevation
  - *Ensure oxygenation*: Normoxia (PaO_2 > 60 mm Hg, SpO_2 > 94%)
  - *Ensure adequate circulating volume*: Normovolemia
  - Maintain normal MABP
  - Ventilation to achieve $PaCO_2$ 35 mm Hg
  - *Osmotic diuretic*: Mannitol 0.25–0.50/kg IV over 20 minutes, repeat SOS (if necessary), or hypertonic (3%) saline infusion: 10 mL/kg bolus, followed by 0.1−1.0 mL/kg/hr
  - Dexamethasone 1–2 mg/kg IV Q6h—cytotoxic cerebral edema (brain abscess, granuloma, tumor)
  - CSF drainage—obstructive hydrocephalus
  - Prevent all events that increase ICP
  - Fever/hypothermia, pain adequate sedation—analgesia, seizures—anticonvulsant, loud noise, invasive stimuli
- *Second-tier therapy*
  - Hyperventilation ($PaCO_2$ 30–35 mm Hg)
  - Barbiturates coma—thiopental or pentobarbital
  - Moderate hypothermia (32–34°C)
- *Third-tier therapy*
  - Decompressive craniectomy or temporal lobectomy
  - Profound hyperventilation to $PaCO_2$ < 30 mm Hg (use transiently)

(PaO_2: Partial pressure of arterial oxygen; SpO_2: Oxygen saturation measured by pulse oximetry; MABP: Mean arterial blood pressure; $PaCO_2$: Partial pressure of arterial carbon dioxide; IV: Intravenous; CSF: Cerebrospinal fluid; ICP: Intracranial pressure).

by mansdocs.com

hyperosmolar therapy, and mild hyperventilation and placement of an ICP monitor. Second and third-tier therapies include lumbar drainage of CSF, high-dose barbiturates, decompressive craniectomy and hypothermia; these treatments are reserved for increased ICP that does not respond to first-tier therapies. Much of these treatment principles and guidelines are extrapolated from studies on adult patients and patients with TBI. A few studies have directly evaluated treatment of raised ICP in children.

Airway, Breathing and Circulation

Meticulous multidisciplinary management of critically ill patients is paramount to the success of any intensive care unit. In patients who are at high risk for raised ICP but do not have overt signs of herniation, the basic tenets of acute resuscitation should be kept in mind.

Airway

In unconscious patients, proper positioning of the head or positioning the patient on the side and suctioning of the oral secretion would ensure airway patency. Oropharyngeal or nasopharyngeal airways can be used. Indications for endotracheal intubation are:

- Modified GCS less than or equal to eight
- Patients with signs of respiratory distress
  - Declining O_2 saturation and increasing O_2 requirement
- Patients unable to protect airway
- Signs of inadequate ventilation and oxygenation such as irregular respiratory efforts, inadequate chest movements, poor air entry, central cyanosis.

Rapid sequence induction (RSI) accompanied by cricoid pressure (Sellick maneuver) is preferred for emergency intubation to prevent aspiration and sudden surge in ICP. The medications that facilitate intubation without increasing the ICP should be used. Monitor heart rate, BP, SpO_2 (oxygen saturation measured by pulse oximetry), provide 100% O_2 and bag ventilation as tolerated by patient and if no airway contraindications, administer sedation and neuromuscular blocking agents: midazolam [0.2–0.3 mg/kg intravenous (IV)], morphine (0.1 mg/kg IV)/fentanyl (5–10 μg/kg IV), and lidocaine 1-1.5 mg/kg IV) and short acting nondepolarizing neuromuscular blocking agents (vecuronium 0.1 mg/kg IV/atracurium 0.5 mg/kg IV/rocuronium 0.6–1.2 mg/kg IV). Ketamine and succinylcholine should be avoided.

Breathing

Maintain normoxia and normocarbia; 100% O_2 should be started with non-rebreathing mask and, if needed, bag valve mask ventilation to ensure adequate oxygenation. Mild short-term hyperventilation should be undertaken if danger of impending herniation is present (unequal pupils, posturing). To achieve this with manual ventilation, administer double the normal breathing rate for given age for 10 minutes duration. Monitor reversal of unequal pupils, posturing and improvement in mentation. Target $PaCO_2$ is approximately 30–32 mm Hg. There is no role for prophylactic hyperventilation.

Circulation

Maintain euvolemia; if there are signs of poor perfusion, give a bolus of normal saline 20 mL/kg. Maintain MABP to achieve desired CPP, if needed by using fluid and vasoactive agents (dopamine, norepinephrine). Colloids are not recommended in acute brain injury (except in acute ischemic stroke) due to their adverse effect on survival.

GENERAL MEASURES

Prevention or treatment of factors that may aggravate or precipitate intracranial hypertension should be undertaken. Specific factors that may aggravate intracranial hypertension include obstruction of venous return (head position, agitation), respiratory problems (airway obstruction, hypoxia, hypercapnia), fever, severe hypertension, hyponatremia, anemia and seizures.

Head Elevation and Position

Elevation of the head end of the bed and keeping the head in a neutral position are standard recommendations to minimize resistance to venous outflow and promote displacement of CSF from the intracranial compartment to the spinal compartment. Elevation of the head up to 30° reduces ICP and increases CPP, but does not change brain tissue oxygenation. The child must be euvolemic prior to placing in this position to avoid orthostatic hypotension. When head elevation is used, the pressure transducers of ICP must be zeroed at the same level (at the level of the foramen of Monro) for intraventricular catheter only (not for intraparenchymal catheter), to assess CPP accurately.

Management of Respiratory Failure

Controlled ventilation may be needed for optimal management and to maintain normal carbon dioxide (CO_2).

by mansdocs.com

During mechanical ventilation high positive end expiratory pressure (PEEP) can increase ICP by impeding venous return and increasing cerebral venous pressure, and by decreasing BP leading to a reflex increase of CBV. The effects of PEEP on ICP also depend on lung compliance; minimal effect is seen when lung compliance is low. Ventilator settings should be adjusted to the optimal setting required to maintain a target O_2 saturation, PaO_2, $PaCO_2$ and physiologic PEEP of 5 cm H_2O. The mode of ventilation should be selected based on patient response and comfort.

Sedation and Analgesia

There are no randomized controlled studies comparing sedation methods in children with acute neurological injury. In general, benzodiazepines have no effect on ICP, whereas the opiates have been reported to increase ICP in adult patients with TBI. One consideration in the choice of sedative should be to minimize effects on BP because most available agents can decrease BP. Hypovolemia predisposes to hypotensive side effects and should therefore be corrected before administering sedatives. Use midazolam 1–3 μg/kg/min, morphine 0.1 mg/kg/dose every 6 hours (Q6h). Sedative doses have to be individualized and titrated to achieve Ramsay sedation scale score of 3–4. At score 3, the patient responds to commands only and at score of 4 the patient is asleep, but has brisk response to glabellar tap or loud auditory stimulus.

Temperature Control

Fever increases metabolic rate by 10–13% per degree Celsius and is a potent cerebral vasodilator. Keep the temperature below 38°C (36–37°C axillary). If child is febrile, use paracetamol 15 mg/kg/dose oral or IV Q4h and surface cooling.

Hypertension

Increase in BP is common in response to raised ICP. Characteristically, rise in systolic BP is greater than diastolic BP. When autoregulation is impaired, hypertension may increase CBF and ICP and may exacerbate cerebral edema and postoperative intracranial bleeds. Generally, it is left untouched in acute raised ICP unless underlying cause is hypertensive encephalopathy. Treatment is also reasonable in patients with impending congestive cardiac failure, those with evidence of rapidly worsening brain edema on CT scan and those with a persistent extreme surge in BP. If it is decided to treat hypertension, vasodilating drugs, such as nitroprusside, nitroglycerin and nifedipine, should be avoided; these could increase ICP. Sympathomimetic-blocking drugs (esmolol, labetalol) or centrally acting alpha-receptor agonists (clonidine) are preferred because they reduce BP without affecting ICP.

Glucose Control

Strict glucose control is essential for the management of acutely injured brain, as hyperglycemia has been correlated with poor outcome. Intensive insulin therapy to keep the blood glucose level between 80 mg/dL and 110 mg/dL is shown to improve outcome and reduce mortality in medical and surgical intensive care units. However, clinical studies have shown that intensive systemic glucose lowering reduces brain glucose concentration, a risk factor for poor outcome. Currently, a less aggressive glucose target of 80–140 mg/dL is recommended for patients with acute brain injury. A continuous insulin infusion should be started if two subsequent random blood glucoses within 6 hours show values above 140 mg/dL, as this level has been found to discriminate between good and bad outcome in neurocritically ill patients; otherwise, a regular insulin sliding scale regimen may suffice.

Treatment of Anemia

Both anemia and transfusion may negatively influence clinical outcome. However, the appropriate transfusion trigger remains unclear and there is great variance in how these patients are transfused. Maintain hemoglobin (Hb) concentration around 10 g/dL to help cerebral O_2 delivery. In cases with severe anemia, a marked increase in CBF occurs to maintain cerebral O_2 delivery. There is evidence from positron emission tomography (PET) and microdialysis studies in humans that transfusion can favorably influence brain metabolism and oxygenation. This correction of hypoxia or altered metabolism rather than anemia may be of greater importance. Results from general critical care should not be extrapolated to all patients with acute brain injury. Transfusion is not risk free but the use needs to be considered also in terms of potential benefit.

Prevention of Seizures

Seizures increase cerebral metabolic rate and lead to a dramatic rise in ICP, but there is no clear relationship

by mansdocs.com

between the occurrence of early seizures and a worse neurologic outcome. Consider seizure prophylaxis in patients at high risk of seizures such as those with severe head injury, focal symptoms and signs, and CNS infections (meningitis and encephalitis). Use phenytoin 20 mg/kg IV loading, followed by 5 mg/kg/day for the first 7 days only. Comatose children should also be considered for electroencephalograph (EEG) monitoring and seizure prophylaxis as nonconvulsive seizures are not uncommon in them. These can cause sudden surge in ICP.

Before Painful Stimuli and Gastrointestinal Prophylaxis

Use lidocaine 1 mg/kg/dose, 5 minutes before endotracheal suctioning and procedure [IV and endotracheal tube (ET)]. Do not repeat within 2 hours. Use antacid 1 mL/kg/dose Q8h or pantoprazole 1 mg/kg/dose Q12h [if gastrointestinal (GI) bleed is present, use pantoprazole].

Glycerol and Corticosteroids

It is not used for acute reduction of raised ICP. However, oral glycerol (6 g/kg/day, 6 hours for 2 days) has been shown to improve outcome in children with acute meningitis. Corticosteroids are commonly used for primary and secondary brain tumors to decrease vasogenic edema. The most commonly used regimen is IV dexamethasone 0.15 mg/kg/dose every 6 hours (maximum 16 mg/day). Routine use in TBI is not recommended.

MEASURES FOR REFRACTORY RAISED INTRACRANIAL PRESSURE

For patients with sustained ICP elevations greater than 20–25 mm Hg, additional measures are needed to control the ICP.

Hyperosmolar Therapy

Two osmotic agents are currently in use in most neurocritical care units: mannitol and hypertonic saline (HTS). Both are highly effective in reducing acutely elevated ICP in various clinical conditions with almost immediate effect lasting for several hours.

Mannitol (20%)

Mannitol is the preferred osmotic agent due to its availability and physician's familiarity of use. Mannitol has rheologic and osmotic effects. Early effect includes reduction of blood viscosity with improvement in microvascular CBF, cerebral oxygenation and CPP with reduction in CBV, ultimately lowering of ICP. Late effect that occurs within 15–30 minutes and lasts up to 6 hours results from direct osmotic effect on neural cells with reduction in total brain water. Additional effects include reduced CSF production. For optimal effect, serum osmolality should be maintained below 320 mOsmol; standard dosage: 0.5 g/kg IV bolus (range 0.2–2 g/kg). Do not repeat mannitol in less than 4 hours. Monitor the urine output and take care of hypovolemia. Mannitol is contraindicated in decompensated shock, oliguria, anuria and heart failure. Repeated doses of mannitol require ICP monitoring since the effect diminishes over time and a rebound phenomenon has been noted after prolonged use. The osmolar gap correlates better with the mannitol level and is the preferred monitoring parameter to prevent mannitol-induced renal failure.

Hypertonic Saline (3%)

Hypertonic saline creates an osmotic force to draw water from the interstitial space of the brain parenchyma into the intravascular space. It promotes rapid CSF absorption, increases cardiac output and expands intravascular volume thereby augmenting the CPP with a positive inotropic effect. Standard dosage: for continuous infusion, 3% HTS is preferred via central line. Usual dose is 10 mL/kg as a loading, followed by 0.1–1 mL/kg/hour. In cerebral edema, the initial serum sodium goal is commonly set at 145–155 mEq/L and is intensified up to 160 mEq/L, if clinically indicated. In general, it is well tolerated and complications are rare. Monitor serum sodium and creatinine every 6 hours. It is contraindicated if serum sodium is greater than 150 mEq/L and/or osmolality greater than 320 mOsmol/L. Therapy must be tapered after 24 hours of continued infusion to prevent rebound rise of ICP. Adverse effects of HTS administration include hematologic and electrolyte abnormalities such as bleeding secondary to decreased platelet aggregation and prolonged coagulation, hypokalemia and hyperchloremic acidosis.

It is unclear which of these two therapies is superior for reduction of ICP. HTS is effective in reducing raised ICP, but does not have clear survival or outcome benefit. A recent systematic review found that HTS appears to achieve a greater reduction in ICP than other osmotic

by mansdocs.com

agents in TBI and in one series of nontraumatic encephalopathies; there was less mortality with use of HTS as compared to mannitol.

Heavy Sedation and Paralysis

Routine paralysis of patients with severe raised ICP is not indicated; however, intracranial hypertension caused by agitation, posturing or coughing can be prevented by deep sedation and nondepolarizing muscle relaxants that do not alter cerebrovascular resistance. A commonly used regimen is morphine and lorazepam for analgesia/sedation and cisatracurium or vecuronium as a muscle relaxant with the dose titrated by twitch response to stimulation and to achieve the Ramsay sedation score 5, which corresponds to state where child is asleep and has sluggish response to glabellar tap. The disadvantage of this therapy is that the neurologic examination (*see* Flowchart 1) cannot be monitored closely. The sedatives and muscle relaxants can be interrupted once a day, usually before morning rounds, to allow neurologic assessments. Since the use of neuromuscular block will eliminate motor activity associated with seizures, but not brain epileptiform activity, children at high risk for seizures should have continuous EEG monitoring.

Hyperventilation

Hyperventilation decreases $PaCO_2$, which induces constriction of cerebral arteries; the resulting reduction in CBV decreases ICP. Acute hyperventilation decreases global CBF. Sometimes this reduction in flow could be sufficient to induce ischemia in injured brain. Hyperventilation has limited use in the management of intracranial hypertension because its effect on ICP is time limited. The vasoconstrictive effect on cerebral arterioles lasts only 11–20 hours because the pH of the CSF rapidly equilibrates to the new $PaCO_2$ level. As the CSF pH equilibrates, the cerebral arterioles redilate possibly to a larger caliber than at baseline, and a possible rebound phase of increased ICP. The precise relationship between hyperventilation and outcome has not been studied in children with raised ICP of any etiology. Based on current evidence, following suggestions can be made:

- Prophylactic hyperventilation should be avoided.
- Mild hyperventilation ($PaCO_2$ 30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to sedation and analgesia, neuromuscular blockade, CSF drainage and hyperosmolar therapy.
- Aggressive hyperventilation ($PaCO_2$ <30 mm Hg) titrated to clinical effect may be considered as a second-tier option in the setting of refractory hypertension and for brief periods in cases of cerebral herniation or acute neurologic deterioration.

Metabolic Suppression Therapy

In patients with preserved flow-metabolism coupling, barbiturate-induced cerebral metabolic suppression is an effective way of reducing ICP refractory to osmotherapy. Barbiturates reduce cerebral metabolism with concomitant reduction in CBF thereby decreasing ICP. In addition, barbiturates have neuroprotective properties including free radical scavenger function, apoptosis inhibition, and reduction in intracerebral pyruvate, and lactate production. Pentobarbital is given in a loading dose of 10 mg/kg, followed by 5 mg/kg each hour for three doses.

Induced Hypothermia

Induced hypothermia is effective in reducing ICP from multiple causes by suppressing all cerebral metabolic activities, thereby reducing CBF. Surface cooling or endovascular cooling catheter may be used to induce mild (34–36°C) to moderate (32–34°C) hypothermia. Surface cooling with a body vest is the preferred method due to its noninvasive nature and relative efficacy in achieving the temperature goal. The endovascular cooling catheter has the advantage of faster time to target temperature but is associated with the risk of infection, bleeding and intravascular thrombosis. Neuromuscular blocking agents and sedatives must be used during hypothermia to prevent shivering.

Surgical Modalities

Decompressive craniectomy may be a useful option for control of increased ICP in children. Craniectomy, performed within the first 24 hours after severe head injury and in refractory raised ICP due to CNS infections, may improve outcomes. Intracranial masses producing elevated ICP should be removed when possible. Acute epidural and subdural hematomas are hyperacute surgical emergencies. Brain abscess must be drained and pneumocephalus must be evacuated. Surgical

by mansdocs.com

management of spontaneous intracerebral bleeding is controversial. CSF drainage lowers ICP immediately by reducing intracranial volume and in long-term by allowing edema fluid to drain into the ventricular system or ventricular peritoneal shunt.

Cerebral Perfusion Pressure Targeted Protocols

The conventional approach in management of raised ICP aims at reducing ICP below 20 mm Hg. Emerging evidence, however, favors CPP targeted therapy wherein the paradigm is shifting to target optimum CPP. It is believed that a certain minimum CPP is needed to maintain adequate supply of O_2 and essential nutrients to brain. What should this minimum be and whether this minimum should be adjusted according to a child's age remain unclear. A review of available studies in pediatric TBI suggests that a minimum CPP of 40 mm Hg may be considered. A CPP threshold 40–50 mm Hg may be considered. There may be age-specific thresholds with infants at the lower end and adolescents at the upper end of this range. CPP less than 40 mm Hg is associated with high risk of death.

BIBLIOGRAPHY

1. Adamo MA, Deshaies EM. Emergency decompressive craniectomy for fulminating infectious encephalitis. J Neurosurg. 2008;108(1):174-6.
2. Allen BB, Chiu YL, Gerber LM, et al. Age-specific cerebral perfusion pressure thresholds and survival in children and adolescents with severe traumatic brain injury. Pediatr Crit Care Med. 2014;15(1):62-70.
3. Bansal A, Singhi SC, Singhi PD, et al. Non traumatic coma. Indian J Pediatr. 2005;72(6):467-73.
4. Crutchfield JS, Narayan RK, Robertson CS, et al. Evaluation of a fiberoptic intracranial pressure monitor. J Neurosurg. 1990;72(3):482-7.
5. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry. 2004;75(6):813-21.
6. Dean JM, McComb JG. Intracranial pressure monitoring in severe pediatric near-drowning. Neurosurgery. 1981; 9(6):627-30.
7. Diringer MN. New trends in hyperosmolar therapy? Curr Opin Crit Care. 2013;19(2):77-82.
8. Frontera JA, Fernandez A, Claassen J, et al. Hyperglycemia after SAH: predictors, associated complications, and impact on outcome. Stroke. 2006;37(1):199-203.
9. Gwer S, Gatakaa H, Mwai L, et al. The role for osmotic agents in children with acute encephalopathies: a systematic review. BMC Pediatr. 2010;10:23.
10. Knapp JM. Hyperosmolar therapy in the treatment of severe head injury in children: mannitol and hypertonic saline. AACN Clin Issues. 2005;16(2):199-211.
11. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med. 2012;13(Suppl 1):S1-82.
12. Kumar G, Kalita J, Misra UK. Raised intracranial pressure in acute viral encephalitis. Clin Neurol Neurosurg. 2009;111(5):399-406.
13. Latorre JG, Greer DM. Management of acute intracranial hypertension: a review. Neurologist. 2009;15(4):193-207.
14. LeRoux P. Haemoglobin management in acute brain injury. Curr Opin Crit Care. 2013;19(2):83-91.
15. Lindvall P, Ahlm C, Ericsson M, et al. Reducing intracranial pressure may increase survival among patients with bacterial meningitis. Clin Infect Dis. 2004;38(3):384-90.
16. Lundberg N, Troupp H, Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. J Neurosurg. 1965;22(6):581-90.
17. Marcoux KK. Management of increased intracranial pressure in the critically ill child with an acute neurological injury. AACN Clin Issues. 2005;16(2):212-31; quiz 270-1.
18. Marmarou A, Fatouros PP, Barzó P, et al. Contribution of edema and cerebral blood volume to traumatic brain swelling in head-injured patients. J Neurosurg. 2000;93(2): 183-93.
19. Meyer MJ, Megyesi J, Meythaler J, et al. Acute management of acquired brain injury part I: an evidence-based review of non-pharmacological interventions. Brain Inj. 2010; 24(5):694-705.
20. Meyer MJ, Megyesi J, Meythaler J, et al. Acute management of acquired brain injury part II: an evidence-based review of pharmacological interventions. Brain Inj. 2010;24(5): 706-21.
21. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology. 2001;56(12):1746-8.
22. Ng I, Lim J, Wong HB. Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. Neurosurgery. 2004;54(3):593-7; discussion 598.
23. Ramesh Kumar R, Singhi SC, Singhi P. Raised intracranial pressure (ICP): management in emergency department. Indian J Pediatr. 2012;79(4):518-24.
24. Shetty R, Singhi S, Singhi P, et al. Cerebral perfusion pressure—targeted approach in children with central nervous system infections and raised intracranial pressure: is it feasible? J Child Neurol. 2008;23(2):192-8.
25. Singhi SC, Khetarpal R, Baranwal AK, et al. Intensive care needs of children with acute bacterial meningitis: a developing country perspective. Ann Trop Paediatr. 2004;24(2): 133-40.
26. Singhi SC, Tiwari L. Management of intracranial hypertension. Indian J Pediatr. 2009;76(5):519-29.

by mansdocs.com

27. Sundbärg G, Nordström CH, Messeter K, et al. A comparison of intraparenchymatous and intraventricular pressure recording in clinical practice. J Neurosurg. 1987;67(6):841-5.
28. Taneda M, Kataoka K, Akai F, et al. Traumatic subarachnoid hemorrhage as a predictable indicator of delayed ischemic symptoms. J Neurosurg. 1996;84(5):762-8.
29. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449-61.
30. Zabramski JM, Whiting D, Darouiche RO, et al. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. J Neurosurg. 2003;98(4):725-30.

by mansdocs.com

SECTION 9

Infections

by mansdocs.com

by mansdocs.com

CHAPTER 49

Extended Spectrum Beta Lactam Producing Infections in Intensive Care Unit

Afzal Azim, AK Baronia

INTRODUCTION

Critically ill patients are prone to nosocomial infections, though the epidemiology of infective organisms depends on the patient cohort. The increased risk of nosocomial infections results from:

- Intrinsic risk factors like malnutrition, extremes of age, comorbidities immunosuppression
- Use of invasive devices and
- Animate reservoirs (e.g. colonized or infected patients).

Outbreaks are common in high-risk areas and may not strictly be restricted to intensive care unit (ICU). Clinicians, microbiologists, infectious disease specialists, and hospital epidemiologists have recognized it as a public health problem.

Betalactam antibiotics comprises of penicillin, monobactam, cephalosporin and carbapenem. Production of β-lactamase enzymes is the most common antimicrobial resistant mechanism in Gram-negative bacteria (GNB). These enzymes hydrolyze the β-lactam ring. In the 1960s and 1970s, resistance to early β-lactams in GNB was reported.

The response to these broad-spectrum β-lactamases led to development of extended-spectrum third-generation cephalosporins such as ceftriaxone, cefotaxime, ceftazidime and monobactams like aztreonam, and carbapenems, which are stable in the presence of the broad-spectrum β-lactamases. By 1980s, GNB responded to these new antimicrobials by developing mutations in the temoneira (TEM) and sulphydryl variable (SHV) β-lactamases, resulting in the evolution of "extended-spectrum β-lactamases" (ESBLs). ESBLs are capable of hydrolyzing penicillins, cephalosporins of the first, second, third and fourth generations, and the monobactam antibiotic aztreonam. Since the 1980s, more than 300 different types of ESBL enzymes, the most common being of the TEM, SHV, CTX-M, and OXA families have been recognized. Though there is no consensus but by definition, ESBLs can be inhibited by β-lactamase inhibitors such as clavulanic acid.

However, clinical isolates of ESBL-producing organisms are frequently found to be resistant to available β-lactam/β-lactamase inhibitor (BL+BLI) combinations. This may be due to hyperproduction of β-lactamases, coproduction of inhibitor resistant β-lactamases, or the combination of β-lactamase production and porin loss. These drugs may be useful in treatment of urinary tract infections due to susceptible strains.

Extended-spectrum β-lactam-producing bacteria can be resistant to antibiotics which include quinolones, aminoglycosides and sulfamethoxazole. Resistance genes or gene clusters can be transmitted horizontally between organisms, as well as between species. These MDR organisms are difficult to be identified by routine laboratory assay methods, which can delay timely initiation of appropriate antimicrobial therapy. Limited availability of antibiotics has laid more importance to preventive strategies and institution of infection control measures and antibiotic Stewardship programs.

ESBL CLASSIFICATION

The first classification was given in 1970 by Jack and Richmond. Subsequently 15 years later, a major reorganization

by mansdocs.com

was proposed by Bush in 1989 with further updating in 1995. The revised Bush scheme classifies β-lactamases by their substrate preference amongst penicillin, oxacillin, carbenicillin, cephaloridine, expanded-spectrum cephalosporins and imipenem, and by their susceptibility testing to inhibition by clavulanic acid. Increasingly, therefore, β-lactamases are classified by sequence, as first proposed by Ambler, recognizing only four classes, designated A to D. Classes A, C and D comprise evolutionarily distinct groups of serine enzymes, and class B contains the zinc types.

TYPES OF ESBL

- *SHV*: SHV-1 is a β-lactamase with activity against penicillins and narrow-spectrum cephalosporins such as cephalothin and cephaloridine. SHV-1 is also common as a plasmid-mediated-lactamase among GNB. A number of SHV variants with ESBL activity are described.
- *TEM*: TEM-1, has inhibition profiles similar to those of SHV-1. More than 150 TEM-type β-lactamases have been described. Ampicillin resistance in isolates of *Escherichia. coli* is due to the production of TEM-1 in most cases.
- *CTX-M*: In 1989, a clinical *E. coli* isolate that produced a non-TEM, non-SHV ESBL was recovered and the enzyme was designated CTX-M-1, showing its hydrolytic activity against cefotaxime. More than 80 CTX-M enzymes have been described till date and are divided into different subgroups.

ESBL IS A GLOBAL PROBLEM

USA

SENTRY study showed a rising percentage of ESBLs in *Klebsiella pneumoniae* in US centers (7.6%). The National Nosocomial Infections Surveillance Systems (NNISS) report 2004 showed rates of *K. pneumonia* resistant to third generation cephalosporins. Data from the MYSTIC program (ESBL production from *K. pneumoniae* and *E. coli* isolates over a 5-year period from 1999 to 2004) showed ESBL prevalence, with less than 1.5% of *E. coli* strains producing ESBLS from 2001 to 2004. A similar low resistance level was seen in *Klebsiella* spp. over the same time period, 2.4–4.4% of strains producing the enzymes.

Europe

Data from the European Antibiotic Resistance Surveillance System (EARSS) also shows increasing prevalence of ESBLs across Europe during the last few decades. TEM and SHV were the predominant ESBL types.

South America

Extended-spectrum β-lactamases in South America rank amongst the highest in the world, with CTX-M dominance. *Klebsiella* isolates producing ESBLs range from 45% to 51%. Similarly, high rates are seen amongst *E. coli* isolates ranging from 8.5% to 18%.

Asia

In Asia, high rates of ESBL were first highlighted by the SENTRY antimicrobial surveillance program (1998–1999) with a large variation in prevalence rates and genotypes. In China, ESBL production from *E. coli* isolates ranged from 13% to 15%, with even higher rates amongst *Klebsiella* (20–60%). Reports from Japan and Taiwan suggest CTX-M genotype as the most prominent.

India

In India ESBLs vary from 30% to 80% in different centers. The Indian Antimicrobial Resistance Study Group and SMART trial 2009 (Surveillance for Monitoring Antimicrobial Resistance Trends) showed high rates of β-lactamase resistance in *E. coli* and *Klebsiella*. ESBL-producing strains were noted in over 60% *E. coli* and more than 55% in *K. pneumoniae* in few centers.

Africa

There is a lack of comprehensive data regarding ESBL-producing Enterobacteriaceae in African countries. The CTX-M genotype appears to be the most common type in North Africa.

WHAT ARE THE RISK FACTORS FOR ESBL INFECTIONS?

Several risk factors have been identified in patients requiring ICU admission.

- *Host factors which predispose to ESBL infections include*:
  - Age more than 60 years
  - Comorbidities (diabetes, coronary artery disease, cerebrovascular disease, chronic liver disease and chronic renal insufficiency)
  - Immunosuppression (chemotherapy, steroids)

by mansdocs.com

  - Prior history of hospitalization (< 6 months)
  - Previous history of ICU admission
  - Prior use of antibiotics (exposure to cephalosporins)
  - Poor functional status.
- *Current hospitalization with risk factors include*:
  - Severity of illness (high APACHE-II and SOFA score)
  - Need for mechanical ventilation
  - Invasive catheters (urinary catheters, central lines, dialysis catheters, etc.)
  - Colonization with MRSA and VRE
  - Use of histamine 2 receptor antagonists
  - Length of stay.
- *Antibiotic selection*:
  - Injudicious use of antibiotics (Practice of polypharmacy)
  - Prolonged course of antibiotics
  - Vancomycin may be a risk factor through relative decolonization of the normal flora due to vancomycin exposure and then subsequent colonization.

ANTIBIOTIC STRATEGIES FOR ESBL INFECTIONS

Various infections caused by ESBL-producing bacteria may include:

- Urinary tract infection
- Bacteremia
  - Primary or secondary
- Respiratory tract infection
  - Nosocomial pneumonia
  - Ventilator associated pneumonia
- Gastrointestinal tract infection
  - Intra-abdominal abscess
  - Peritonitis
  - Cholangitis
- Skin and soft tissue infection
- Catheter or device related infection
- Sinusitis
- Neurosurgical meningitis
  - Related to ventricular drainage catheters.

Best principles for optimization of antibiotic include:

- Awareness of local microbiological flora with regular update
- Source control and drainage of abscesses, empyema cavities, and other infected fluid collections
- Removal of infected intravascular catheters (e.g. central venous catheters) whenever there is suspicion of catheter related infections
- Use the concept of pK/pd
- Minimize duration of antibiotic use which promotes resistance
- Consider de-escalation on available microbiologic data and clinical course.

Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society for Healthcare Epidemiology of America (SHEA), and the Paul Ehrlich Society of Chemotherapy regarding appropriate treatment of serious bacterial infections have advocated the use of initial empirical therapy with broad-spectrum antimicrobials.

Adopting these guidelines, the risks of death, morbid complications, duration of hospital stay, and emergence of resistance (due to extended treatment with broad-spectrum agents) are lowered.

ANTIBIOTIC SELECTION

Carbapenems

Carbapenems are Antibiotics of Choice

In a study with ESBL-producing *K. pneumoniae* bacteremia, the 14-day mortality rate associated with inappropriate treatment was 63.6%, and that associated with isolate-susceptible treatment was 14.1%. The 14-day mortality rate among patients who received a carbapenem within 5 days after the first blood culture result was obtained was 4.8% and 27.6% among patients who received noncarbapenem antimicrobials. Use of a carbapenem was an independent predictor of decreased mortality.

Studies have shown that for patients with ESBL-producing *E. coli* or *K. pneumoniae* bacteremia, 30-day mortality rates are lowest among those who receive a carbapenem (12.9%) or ciprofloxacin (10.3%), and administration of a broad-spectrum cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, or ceftazidime). In a prospective cohort study of 43 patients with *E. coli* bacteremia producing ESBL, the mortality rate with a BL+BLI or a carbapenem regimen was 9%, compared with a mortality rate of 35% among those who received empirical treatment with cephalosporin or a fluoroquinolone. Moreover, 78% of patients treated with a cephalosporin or fluoroquinolone required changes in therapy after culture results became available.

Based on current evidence, it is recommended that a critically ill patient with a high possibility of ESBL-*K. pneumoniae* or *E. coli* infection should be treated

by mansdocs.com

empirically with a carbapenem. Imipenem and meropenem are equally efficacious in their activity against ESBL-*K. pneumoniae*.

Cephalosporins

- Not recommended as first line of drugs.
- May fail due to inoculum effect.

The use of any third- and fourth-generation cephalosporin for the treatment of serious infections due to ESBL-producing Enterobacteriaceae is not recommended due to high failure rates caused by strains with MIC values of 2–8 μg/mL. For laboratories that are implementing the new 2010 Clinical and Laboratory Standards Institute guidelines, the question will arise as to whether cefepime or other agents can now be used for an ESBL-producing organism if it is susceptible with an MIC of less than 1 μg/mL.

Another theoretical concern for use of cefepime for the treatment of ESBL-producing organisms is the "inoculum effect". In vitro, concentrations of ESBL-producing bacteria higher than those used in routine susceptibility testing produce more β-lactamase and hydrolyze cefepime more effectively. The inoculum effect is less with piperacillin-tazobactam or carbapenems.

Cephamycins

Cephamycins are not recommended as first-line therapy for ESBL producing organisms, despite their good in vitro Activity: There are few published reports of the use of cephamycins (for example, cefoxitin and cephamycin) in the treatment of ESBL producers. In one of these reports, selection of porin resistant mutants occurred during therapy, resulting in relapse of infection. In addition, combined cephamycin and carbapenem resistance in *K. pneumoniae* has been observed in the setting of widespread cephamycin use in response to an outbreak of infection with ESBL producing organisms.

Use of Beta-lactam with Beta-lactamase Inhibitors for ESBL Infections

Combination of beta-lactam with beta-lactamase can be used in patients with ESBL infections if they are suffering from mild infections (inoculum is low, and patient is not in severe sepsis and septic shock).

- *Clavulanic acid*: It is available as two combinations amoxicillin clavulanate and ticarcillin clavulanate. Amoxicillin clavulanate was the first BLI used in clinical practice. Ticarcillin-clavulanate is available as parenteral preparation and interestingly has activity against multidrug resistant *Stenotrophomonas maltophilia*.

  There are concerns for the emergence of AmpC β-lactamase-producing bacteria with the use of clavulanate. Recently clavulanate combination with cefepime and cefpirome has been proposed.
- *Sulbactam*: Ampicillin-sulbactam was launched in 1987. Unfortunately resistance to it is increasing among isolates of *E. coli*. Cefoperazone sulbactam is not marketed in the USA. It is frequently used in Europe and India. Plain sulbactam combinations are also available now. The growing popularity of the drug is due to inherent activity against *Acinetobacter*.
- *Tazobactam*: It is available as piperacillin-tazobactam. The combination has synergistic action. It is not much useful when inoculum is high.

Other Antibiotic Choices for Treatment of ESBL Infections

Fluoroquinolones

Coexistence of multiple resistance mechanisms affecting the quinolones are frequent.

Observational clinical studies have compared quinolones and carbapenems for serious infections due to ESBL producing organisms and proved superiority of carbapenems. Suboptimal dosing of quinolones in the presence of strains with elevated MIC (yet remaining in the "susceptible" range) may account for fewer efficacies.

Aminoglycosides

May be potentially useful in the treatment of complicated urinary tract infections due to ESBL-producing organisms but are not recommended as monotherapy. Aminoglycosides are often used in combination with beta-lactam antibiotics for treating serious Gram-negative infections.

Nitrofurantoin or Fosfomycin

These antibiotics are only useful in the treatment of urinary tract infection and their utility continues as reserve drugs.

Tigecycline

It is active against most ESBL-producing strains and is also stable to the effects of carbapenem-hydrolyzing β-lactamases. However, caution needs to be exercised for bloodstream and urinary tract infections given the low drug concentrations at these sites.

by mansdocs.com

Published clinical data on use of tigecycline for serious infections due to ESBL-producing organisms is lacking thus far. This drug should be restricted for organisms resistant to carbapenems.

Colistin and Polymyxin B

Have activity against most ESBL-producing strains. Dosing regimens are not well-established for these antibiotics, especially in critically ill individuals and in patients with renal failure. This antibiotic should be reserved for carbapenem resistant organisms, and its routine use should be avoided.

Preventive Strategies

Extended-spectrum β-lactamase infections can occur as isolated case or as outbreaks. Preventive strategies are designed to prevent outbreaks. Precautions, outlined by the American Centers for Disease Control and Prevention (CDC), as follows:

- General precautions required all healthcare workers to disinfect their hands with an alcohol-based hand cleanser before and after each contact with a patient.
- If hands are visibly soiled, wash them first with soap and water and dry them before rubbing them with an alcohol-based hand-rub solution.
- If contact with a patient's blood or body fluids is likely, precautions should be taken to avoid direct contact with them. Gloves, and if necessary a gown or mask, should be worn.
- After removing the gloves, hands should be disinfected with an alcohol-based hand-rub solution.
- All measures should be taken to avoid needle sticks or cuts.

This strategy should also be used in a larger context, for example when handling laundry, disposing of medical waste and during the daily cleaning of frequently touched surfaces in patients' rooms.

Microbiological Detection of ESBLs in Laboratory

ESBLs Detection Needs more than One Antibiotic Substrate

Screening accuracy depends on the cephalosporin(s) used as a first-line "indicator", the bacterial species and the type of ESBL. To improve the accuracy of ESBL detection, it is advisable to use a combination of at least two indicator cephalosporins. In inducible enterobacterial species (*Enterobacter* spp., *Citrobacter freundii, Serratia marcescens, Providencia* spp.), screening tests are unable to distinguish ESBLs from hyperproduced AmpC chromosomal cephalosporinases.

ESBLs Detection Needs more than One Method

- A screening test that detects resistance or decreased sensitivity to ceftazidime, cefotaxime, ceftriaxone and aztreonam. Since no "indicator" cephalosporin alone is able to detect all types of ESBL, testing several cephalosporins (at least two) is recommended as a first-line procedure.
- A second confirmatory test, based on the synergy between a cephalosporin (cefotaxime or ceftazidime) and a BLI (clavulanic acid), should then be carried out. This test could be a double disk test, combination disk method or ESBL Etest®.

Automated Tests for ESBL Detection

The most routinely used automated systems for bacterial identification and for antibiotic susceptibility testing (VITEK® 2, bioMérieux; Phoenix, BD) include ESBL detection. Automated methods are generally based on CLSI criteria and currently only include ESBL detection for *E. coli*, *Klebsiella* spp. and *P. mirabilis*.

SUMMARY

In recent years, ICUs have witnessed increasing incidence of infections caused by antibiotic-resistant pathogens which includes ESBL-producing Gram-negative bacilli. Studies have demonstrated use of antibiotics, presence of invasive catheters, prior hospitalization, long duration of hospital stay, and the use of extended-spectrum cephalosporin as risk factors for infections caused by ESBL-producing isolates. It is a global phenomenon and centers in India have reported incidence of ESBLs ranging from 30% to 80%.

The threat of potential drug resistance in these infections is a major driver for the selection of empiric antimicrobial regimens. Managing ESBL bacterial infections is a special challenge due to limited antibiotic choice and difficult microbiological diagnosis. Early and appropriate antibiotic initiation is the key to reduce ICU stay, morbidity and mortality. Besides judicious

by mansdocs.com

use of antibiotics, implementation of effective infection control programs and antibiotic Stewardship needs to be incorporated in all ICUs to reduce the incidence of resistant infections. This chapter reviews mechanism of ESBL mediated resistance in GNB, modes of transmission, epidemiology, risk factors, and management of infections caused by these pathogens.

BIBLIOGRAPHY

1. Azim A, Dwivedi M, Rao PB, et al. Epidemiology of bacterial colonization at intensive care unit admission with emphasis on extended spectrum β-lactamase and metallo-β-lactamase producing Gram-negative bacteria–an Indian experience. J Med Microbiol. 2010;59(Pt 8):955-60.
2. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Twentieth informational supplement. CLSI document M100–S20. Wayne (PA): Clinical and Laboratory Standards Institute; 2010.
3. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159-77.
4. Dhillon RH, Clark J. ESBLs: A Clear and Present Danger? Crit Care Res Pract. 2012;2012:625170.
5. Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. Clin Microbiol Rev. 2010;23(1):160-201.
6. Fraimow HS, Tsigrelis C. Antimicrobial resistance in the intensive care unit: mechanisms, epidemiology, management of specific resistant pathogens. Crit Care Clin. 2011; 27(1):163-205.
7. Harris AD, McGregor JC, Johnson JA, et al. Risk factors for colonization with extended-spectrum β-lactamase producing bacteria and intensive care unit admission. Emerg Infect dis. 2007;13(8):1144-9.
8. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant Gram-negative organisms: extended-spectrum β-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, multidrug-resistant Pseudomonas aeruginosa. Mayo Clinic Proceedings 2011;86:250-59.
9. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005; 18(4): 657-86.
10. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Agents Chemother. 2010;54(10):4085-91.

by mansdocs.com

CHAPTER

50

Infections in Immunocompromised Patients in ICU

AK Baronia, Afzal Azim, RK Singh

INTRODUCTION

Life-threatening infections occur frequently in immunocompromised patients with chronic diseases. It has been found that more than half of patients with severe sepsis have at least one chronic comorbidity like complicated diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), or chronic liver disease. Although patients with these conditions do not have primary defects in the immune system, they often have various immune abnormalities that make them prone to specific infections. Life-threatening infections that occur in patients with chronic medical diseases, namely DM, COPD, CKD, cirrhosis, and heart failure (HF), are presented here.

PATHOGENESIS

Common changes in the innate, cell-medicated, and humoral immunity described in patients with these chronic medical conditions are as follows:

- Reduced neutrophil chemotaxis after stimulation
- Functional abnormalities of neutrophils, monocytes, dendritic cells, and lymphocytes in uremia
- Reduced numbers and function of Kupffer cells, impaired phagocytotic function of neutrophils, and down regulation of proinflammatory cytokine production after lipopolysaccharide stimulation in cirrhosis
- Decreased sensitivity of natural killer cells to activation by interleukin (IL)-2 and interferon-γ in HF.

DIABETIC PATIENTS WITH LIFE-THREATENING INFECTIONS

Epidemiology

India has high prevalence of DM. The worldwide DM prevalence is expected to increase to 7.7% by 2030. DM predisposes to critical illness. DM prevalence among critically ill patients in the United States was up to 22.6%; while it was less prevalent (7.2%) in a European cohort of critically ill patients with sepsis.

Specific Infections

Diabetes mellitus is associated with increased risk of urinary tract infections (UTIs), skin and soft tissue infections (SSTIs), and lower respiratory tract infections.

Urinary Tract Infections

Urinary tract infections are among the most common infections that affect diabetic patients and are often complicated. Emphysematous cystitis and pyelonephritis are rare but serious complication of lower UTI and occurs mainly in diabetics. It most commonly occurs due to *Escherichia coli*, followed by other enteric Gram-negative bacilli.

Skin and Soft Tissue Infections

Skin and soft tissue infections are composed of heterogeneous conditions, including simple cellulitis, infected foot ulcer with or without cellulitis, necrotizing fasciitis, deep abscesses, osteomyelitis, and septic arthritis. About

by mansdocs.com

9% of diabetic patients developed foot infections. Fournier gangrene represents a severe form of SSTI that involves the perineal, perianal or genital regions, with 40–60% of patients having DM. Causative pathogens vary which includes, β-hemolytic streptococci and *Staphylococcus aureus* predominate in cellulitis and acute infected foot ulcers. Methicillin-resistant *S. aureus* (MRSA) prevalence has been increasing in infected foot ulcers. Studies from India have also showed increasing prevalence of other multidrug-resistant Gram-negative organisms. Gram-negative bacteria and anaerobes should be considered in chronic and deeper infections and polymicrobial infection should be considered in severe situations. Infecting microorganisms are usually mixed aerobic and anaerobic bacteria.

Fungal Infections

Diabetes mellitus is also a risk factor for fungal infections, including candidiasis and mucormycosis. A population-based surveillance for candidemia found that among diabetic adults, the average annual incidence of candidemia was 28 per 100,000 population. Approximately half of rhinocerebral mucormycosis cases occur in patients with DM.

Management

Antimicrobial Therapy

Diabetes mellitus is considered a risk factor for infections with resistant microorganisms. Hence, empiric therapy should be broad and directed against the suspected causative agents taking into consideration local susceptibility patterns.

Surgical Indications and Therapy

Current evidence suggests that the treatment of choice for emphysematous pyelonephritis is medical management combined with percutaneous drainage. However, nephrectomy may be needed in patients with extensive diffuse gas and renal destruction. Debridement and amputation may be necessary in diabetic foot ulcers with deep infection and gangrene. Necrotizing fasciitis and Fournier gangrene frequently require surgical intervention. Immediate debridement of necrotic tissues is one of the principles of treatment and the most important for improved survival. For mucormycosis, aggressive surgery and long-term therapy with amphotericin B may lead to improved outcomes.

Supportive Therapy

Insulin therapy is essential in the management of infected diabetic patients with hyperglycemia. Optimal glucose control for diabetic and nondiabetic patients is associated with significantly decreased risk of septicemia. Agents used for reducing cardiovascular risk have been evaluated in infected diabetic patients and statin use is associated with reducing pneumonia risk.

Outcome

Certain DM-associated infections are known for their aggressive course and poor prognosis, especially if not treated promptly. Examples include Fournier gangrene and mucormycosis. DM is also associated with increased risk of death after H1N1 infection. Community-acquired pneumonia (CAP) and septicemia in surgical ICU patients.

COPD PATIENTS WITH LIFE-THREATENING INFECTIONS

Epidemiology

Prevalence of COPD is increasing from 3.0% among people aged 18–44 years to more than 10.0% among those aged 65 years or older. The main causes of hospitalization are COPD exacerbation and cardiovascular disease.

Specific Infections

Acute Exacerbation of COPD

Even with therapy, patients with COPD have 1–2 acute exacerbations, on average, each year. Most COPD exacerbations are due to recurrent infections with viral or bacterial pathogens. Viruses may account for more than 50% of exacerbations. Viral COPD exacerbations appear to be more severe and last longer than those without a viral trigger. Although bacteria frequently colonize the airways in COPD, bacterial exacerbations are usually associated with acquiring new bacterial strains of *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

Community-acquired Pneumonia

The COPD course is frequently complicated by CAP. The use of inhaled corticosteroids in patients with COPD has

by mansdocs.com

been implicated in the increased CAP risk. When having CAP, patients with COPD usually present with more severe respiratory failure and higher Pneumonia Severity Index (PSI). *S. pneumoniae* is the most common isolated pathogen, followed by *H. influenzae, P. aeruginosa, S. aureus, M. catarrhalis*, and atypical pathogens. Repeated severe COPD exacerbations are a risk factor for CAP due to *Pseudomonas* species. COPD is also a risk factor for ventilator-associated pneumonia (VAP). *P. aeruginosa*, *Acinetobacter* species, and *S. aureus* are the usual causative organisms. Systemic corticosteroid use increases the risk of infections with multidrug-resistant organisms.

Invasive Pulmonary Aspergillosis

Patients with severe COPD who are receiving broad-spectrum antibiotics and corticosteroids have an increased incidence of invasive pulmonary aspergillosis (IPA). IPA risk factors were ICU admission, receiving antibiotics in the prior 3 months, and corticosteroid therapy in the prior 3 months.

Other Infections

Pneumocystis jiroveci causes opportunistic fungal respiratory tract infections in immunocompromised patients. However, it is a frequent colonizer of the lungs. Patients with COPD are at increased risk for *Pneumocystis* colonization. Infection with this organism should be considered in patients with COPD, especially those on corticosteroids or with nonresolving pneumonias. Patients with COPD are at risk for influenza infections and bacterial coinfections.

Management

Antimicrobial Therapy

Management of acute COPD exacerbation includes the administration of antibiotics, usually in the presence of increased sputum volume and purulence. Antibiotics significantly reduce the treatment failure risk, although the evidence of low quality.

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) has outlined evidence-based clinical practice guidelines for CAP management, which are stratified based on pneumonia severity. For non-ICU inpatients, a respiratory fluoroquinolone or β-lactam plus a macrolide are recommended. For ICU patients, a β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone are recommended. When *Pseudomonas* risk exists, an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin, levofloxacin, or aminoglycoside are recommended. When MRSA risk exists, vancomycin or linezolid should be added.

Voriconazole is the primary IPA treatment. The use of combination therapy remains controversial with some evidence supporting combination antifungal therapy for salvage or failed monotherapy.

Influenza is usually treated with the neuraminidase inhibitors, oseltamivir and zanamivir. For severe cases, it is recommended to increase oseltamivir dosage from 75 mg to 150 mg twice daily. Peramivir, an intravenous neuraminidase inhibitor should be used for the treatment of patients with severe influenza.

Supportive Care

Systemic corticosteroids are used in acute COPD exacerbations, but their role in the management of patients with COPD with pneumonia is less defined. Hyperglycemia may develop and blood glucose control may be needed. Evaluation for adrenal insufficiency and corticosteroid replacement should be considered in severe COPD with frequent exacerbation and corticosteroid use.

Patients with COPD are at increased risk for specific cardiovascular conditions: arrhythmia, angina, acute myocardial infarction, HF, stroke, and pulmonary embolism. Current evidences are there that uses of β-blocker, statin, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker in these patients reduce mortality.

Outcome

Infections in patients with COPD are usually associated with significant morbidity and mortality. Mortality predictors include higher values of acute physiology scoring systems, low Glasgow Coma Scale on ICU admission, cardiac dysrhythmia, and length of hospital stay before ICU admission. In general, the mortality ascribed to CAP in COPD is 4–34%. In VAP, COPD is an independent predictor of ICU mortality. The mortality associated with IPA in patients with COPD is extremely high, reaching 91%.

by mansdocs.com

CKD PATIENT WITH LIFE-THREATENING INFECTIONS

Epidemiology

Chronic kidney disease is a global public health problem. In the United States, about 10% of noninstitutionalized adults are estimated to have CKD. Patients with CKD have high sepsis prevalence and severity. Dialysis-related infections were responsible for 25% of the episodes, followed by below-the-knee SSTI, pneumonia, and other SSTIs. Most infections were acquired in the community.

Specific Infections

Catheter-related Bloodstream Infections

Central venous catheters are the most frequent vascular access for dialysis initiation among patients with incident End-stage renal disease (ESRD). Incidence of catheter-related bloodstream infection (CRBSI) ranges between 0.6 and 6.5 episodes per 1,000 catheter days. CRBSI diagnosis is usually confirmed by isolation of the same microorganism from quantitative cultures of both the catheter and the peripheral blood in a septic patient without any other apparent source. Most CRBSI-causative agents are gram-positive organisms (*S. aureus and S. epidermidis*).

Peritonitis

Peritonitis is a complication of peritoneal dialysis. Cultures are not sensitive enough as these may be sterile. There are possibilities of polymicrobial growth also in culture.

Community-acquired Pneumonia

Patients with CKD usually have more severe CAP, as reflected by higher PSI compared with other patients. The microbiology is similar to non-CKD, with *S. pneumonia* being the most frequent pathogen.

Management

Antimicrobial Therapy

Empiric antimicrobial therapy for CRBSI should include broad-spectrum coverage for both Gram-positive and gram-negative organisms. Owing to the high MRSA prevalence in the hemodialysis setting, empiric therapy should include anti-MRSA coverage with de-escalation when culture results become available. Antimicrobial therapy is usually administered for 7–14 days. The duration is extended to 4–6 weeks if there is persistent bacteremia or fungemia occurring more than 72 hours after hemodialysis catheter removal and for patients with endocarditis or suppurative thrombophlebitis and to 6–8 weeks for the treatment of osteomyelitis. The use of antibiotic catheter lock has been suggested to be instituted when catheter salvage is desired in the absence of exit site and tunnel infection. For the management of peritonitis associated with peritoneal dialysis (PD), a systematic review found that intraperitoneal glycopeptide-based regimens or first generation cephalosporin antibiotics were superior to intravenous antibiotics in reducing treatment failure.

Surgical Indication and Therapy

Patients with tunnel infection or port abscess require removal of the catheter, and incision and drainage if indicated. For CRBSI associated with tunneled hemodialysis access, the catheter should be surgically removed when any of the following conditions is present: severe complications (such as severe sepsis, endocarditis, and suppurative thrombophlebitis), persistent bacteremia or persistent clinical infection signs despite 48–72 hours of appropriate antimicrobial therapy, infection with *S. aureus, P. aeruginosa*, multidrug-resistant organisms, fungi, or mycobacteria. For patients on PD, surgical removal of the PD catheter should be performed in the presence of refractory peritonitis, defined as failure of the effluent to clear after 5 days of appropriate antibiotics.

Supportive Therapy

Early arteriovenous fistula planning and institution may reduce access-related infections. A meta-analysis of 11 trials found that antibiotic catheter lock solutions significantly reduced CRBSI and catheter removal. As such, clinical practice guidelines recommended the prophylactic use of antimicrobial lock solution in patients with long-term catheters who have a history of multiple CRBSIs despite optimal maximal adherence to aseptic technique.

It has been found that sepsis-related hospitalizations were less frequent in CKD patients receiving statins than in those not receiving statins.

Outcome

Infections account for 20% of ESRD deaths, the second most after cardiovascular disease, and sepsis-related-mortality in ESRD is approximately 100-fold to 300-fold higher compared with the general population. In a systematic review, hospital mortality of patients with ESRD

by mansdocs.com

was high compared with matched patients with mild acute kidney injury. Among patients with CKD with CAP, mortality rates are markedly higher in dialysis patients compared with the general population, and prior pneumococcal vaccination is associated with reduced mortality risk. One study of critically ill PD patients, with sepsis due to peritonitis as the most common admitting diagnosis, found a 1-year mortality of 53.0%.

CIRRHOTIC PATIENTS WITH LIFE-THREATENING INFECTIONS

Epidemiology

In the United States, approximately 15% of the population has chronic liver disease, with cirrhosis being a major cause of death worldwide. Life-threatening infections are a major reason for admissions to the hospital and ICU. Cirrhosis-related infections are unique in terms of presentation, outcome, and therapeutic options.

Specific Infections

Patients with cirrhosis may have a different presentation of infections compared with other patients. Studies have shown that up to one-third of patients with cirrhosis fail to develop leukocytosis or a temperature higher than 38° C or lower than 36° C. Patients with cirrhosis have lower baseline blood pressure, and higher heart rate and respiratory rate. Therefore, a complete workup, including a diagnostic paracentesis and ascitic fluid culture, urine and blood cultures, and chest radiograph, should be done soon when sepsis is suspected.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is the most frequent infection in cirrhosis, accounting for 10–30% of all documented bacterial infections in hospitalized patients with cirrhosis. SBP diagnosis should be based on neutrophil count in ascitic fluid of higher than 250/mm^3. Bacterascites is when an ascitic neutrophil count is lower than 250/mm^3 but with a positive ascitic fluid culture and recommends antimicrobial therapy if the patient exhibits signs of systemic inflammation or infection.

The most frequently isolated organisms in SBP are *E. coli, Klebsiella* species, and other Enterobacteriaceae. There is an upsurge in isolation in quinolone-resistant gram-negative bacteria, extended-spectrum β-lactamase and multidrug-resistant gram-positive bacteria. A recent study has shown an increase in *Enterococcus* species, *S. aureus* and *Candida* species, attributed to nosocomial infections and recent antibiotic treatment.

Community-acquired Pneumonia

Bacterial CAP is common in patients with cirrhosis. In fact, cirrhosis is a minor criterion in defining severe CAP. Compared with other patients, patients with cirrhosis more frequently presented with impaired consciousness, septic shock, higher PSI scores (classes IV–V) and bacteremia. *S. pneumoniae* is the most common microorganism, followed by *H. influenzae* and *L. pneumophila*.

Skin and Soft Tissue Infections

The SSTIs constitute approximately 10% of infections in patients with cirrhosis. These infections are caused by both gram-positive and gram-negative bacteria. Cellulitis is the most frequently observed SSTI. Necrotizing fasciitis is less common and is predominantly caused by gram-negative bacilli.

Community-acquired Bacterial Meningitis

Community-acquired bacterial meningitis in patients with cirrhosis is an uncommon but a serious infection. Unfortunately, the diagnosis is often delayed. Patients with cirrhosis with meningitis presented with lower Glasgow Coma Scale and were more likely to have seizure and septic shock. Signs of meningeal irritation may be delayed or absent and mental status changes are often confused with hepatic encephalopathy.

Endotipsitis

Endotipsitis refers to transjugular intrahepatic portosystemic shunt (TIPS) infection. Its definition is still debated, but involves persistent bacteremia and fever together with either shunt occlusion, or vegetation, or bacteremia in the presence of a patent shunt, when other sources of bacteremia have been ruled out.

Management

Antimicrobial Therapy

Empiric antibiotics should be started immediately following the diagnosis of SBP. Because the most common causative organisms of SBP are Gram-negative aerobic bacteria,

by mansdocs.com

it is recommended to use third-generation cephalosporins as the first-line antibiotic treatment with amoxicillin/clavulanic acid and quinolones as alternative options. However, quinolones are not recommended if they are used for SBP prophylaxis, in areas where there is a high prevalence of quinolone-resistance, or in nosocomial SBP. In nosocomial SBP, the incidence of ESBL-producing bacteria, as well as multidrug-resistant gram-positive bacteria such as *Enterococcus faecium* and MRSA, is increasing. Empiric therapy with carbapenems and glycopeptides is suggested in nosocomial infections in which there is high suspicion of multidrug-resistant organisms, with de-escalation as soon as possible.

The management of CAP in patients with cirrhosis follows the same guidelines outlined previously in the COPD section. Given the unique microbiology in this population, it is important for empiric antimicrobial therapy to cover *K. pneumoniae, E. coli, Listeria monocytogenes*, and Pneumococcus. SSTIs should be treated with broad-spectrum antimicrobials with timely surgical intervention for necrotizing fasciitis. The treatment of endotipsitis relies mainly on antimicrobial therapy because infected stent removal is impractical. Broad-spectrum antibiotics to cover both Gram-positive and Gram-negative bacteria should be initiated. Vancomycin plus third-generation cephalosporins have been the most common regimen reported in some series. Carbapenems may be used if there is increased risk of multidrug-resistant organisms. If fungal infection is suspected, antifungal therapy should be started.

In patients with cirrhosis presenting with septic shock, the use of inappropriate initial antimicrobials was found to be related to increased mortality. Additionally, a single rather than two or more appropriate antimicrobials was found to be also associated with higher mortality.

Intravenous Albumin

A randomized, controlled study in SBP patients treated with cefotaxime showed that albumin significantly reduced mortality from 29% to 10% compared with Cefotaxime alone. It is recommended that all patients who develop SBP should be treated with broad-spectrum antibiotics and intravenous albumin.

Low-dose Hydrocortisone Therapy

Relative adrenal insufficiency is very common (more than two-thirds) in patients with cirrhosis in septic shock. In a randomized controlled trial of 75 patients with cirrhosis presenting with septic shock, hydrocortisone therapy resulted in a significant hemodynamic improvement compared to placebo. However, there was no mortality benefit and hydrocortisone therapy was associated with increase shock relapse and gastrointestinal bleeding.

Granulocyte Colony-stimulating Factor

A recent randomized controlled trial compared 5 mg/kg granulocyte colony-stimulating factor (G-CSF) with placebo in 47 patients with acute-on-chronic liver failure and found significant improvement of survival at day 60 and reduction in sepsis incidence. However, a recent meta-analysis of the use G-CSF in patients with severe sepsis and septic shock showed no benefit. Whether, G-CSF has a special benefit in patients with cirrhosis remains unknown.

Outcome

Infections in patients with cirrhosis generally carry a poor prognosis. In-hospital mortality for the first episode of SBP ranges from 10% to 37% and 1-year mortality has been reported to be 31–93%. Similarly, CAP in cirrhosis is associated with 14–30% mortality. Factors associated with mortality include impaired consciousness, multilobar pneumonia, ascites, acute renal failure, bacteremia, ICU admission, and high Model for End-Stage Liver Disease score. Meningitis has a reported mortality of 38–63% in patients with cirrhosis. In patients with cirrhosis who develop septic shock, the mortality reaches 75.0%.

HEART FAILURE PATIENTS WITH LIFE-THREATENING INFECTIONS

Epidemiology

Patients with HF are at increased risk for CAP, a common reason for their hospitalization. Additionally, HF is a risk factor for admission of patients with CAP into the ICU. Patients with HF are at increased risk for influenza infection, including H1N1.

Specific Infections

The diagnostic approach to patients with severe CAP has been outlined earlier (COPD section). If viral pneumonia is suspected, respiratory samples for viral pathogens, including H1N1 polymerase chain reaction, should be obtained. CAP diagnosis in acute HF may be difficult

by mansdocs.com

because of similarity of the two conditions on physical examination and chest radiography. Serum B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide may help to differentiate between these two entities in patients presenting with acute dyspnea. A recent trial in patients presenting to the emergency department with dyspnea found that a model using procalcitonin was more accurate than any other individual clinical variable for pneumonia diagnosis in all patients, and in those with acute HF. The study found that patients with acute HF and an elevated procalcitonin concentration (> 0.21 ng/mL) had a worse outcome if not treated with antibiotics. Thoracic ultrasound demonstrating B-lines that suggests thickened interstitial or fluid-filled alveoli, seen most commonly in patients with HF, have been suggested to further aid in differentiating pneumonia from HF.

Antimicrobial Therapy

Management of CAP in patients with HF follows the IDSA/ATS consensus guidelines as summarized in the COPD section. Patients with suspected severe influenza, including H1N1, should be treated with oseltamivir as soon as possible.

Outcome

A population-based cohort study of adult patients hospitalized for pneumonia found a 30-day mortality of 24.4% among patients with HF compared with 14.4% among other patients and that the severity of HF substantially increased mortality. Similarly, HF is independently associated with increased mortality risk in patients with H1N1 infections.

SUMMARY

Chronic illnesses, such as DM, COPD, CKD, cirrhosis and HF, are often associated with immune abnormalities that make affected patients prone to specific life-threatening infections. Although encountered in patients without chronic illnesses, the presentation and prognosis of these infections are frequently different making physicians' awareness about them crucial for appropriate management. Physicians who care for patients with life-threatening infections should know about the associated chronic illnesses, as these illnesses may affect immune function and predispose patients to specific infections that could be caused by multidrug-resistant or opportunistic organisms. Further studies on the management of life-threatening infections in these patients are needed to understand their special characteristics and determine the specific diagnostic and therapeutic approaches.

BIBLIOGRAPHY

1. Al-Dorzi HM, Khan R, Arabi YM. Life-threatening infections in medically immunocompromised patients. Crit Care Clin. 2013;29(4):807-26.
2. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005; 171(4):388-416.
3. Andreasen AS, Pedersen-Skovsgaard T, Berg RM, et al. Type 2 diabetes mellitus is associated with impaired cytokine response and adhesion molecule expression in human endotoxemia. Intensive Care Med. 2010;36(9):1548-55.
4. Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. Curr Opin Crit Care. 2008;14(2): 189-97.
5. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417.
6. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 200;44 Suppl 2:S27-72.
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1): 1-45.
8. Viasus D, Garcia-Vidal C, Cruzado JM, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. Nephrol Dial Transplant. 2011;26(9):2899-906.
9. Yende S, van der Poll T, Lee M, et al. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. Thorax. 2010;65(10):870-7.

by mansdocs.com

CHAPTER 51

Invasive Fungal Infections in Critically Ill Patients

AK Baronia, Armin Ahmed, Afzal Azim, Mohan Gurjar, Rungmei Marak

INTRODUCTION

Over the past few decades fungal infection is showing a rising trend and increasing prevalence worldwide. A recent large international survey reported prevalence of *Candida* and *Aspergillus* infection 17% and 1.4% respectively in intensive care unit (ICU). Surgical patients tend to have higher rates of fungal infection. Emergence of *Candida* is further complicated by increased rate of infection due to non-albicans species. This epidemiological shift could be due to large use of azole group of antifungal agents. Resistance to various antifungal agents is also of growing concern. Fungal infections are associated with high mortality and morbidity.

Colonization almost invariably precedes *Candida* infection. Frequency of *Candida* infection increases with increased number of sites colonized. Besides immunosuppression, factors known to be associated with increased risk of invasive fungal infections (IFIs) are broad-spectrum antibiotic use, total parenteral nutrition (TPN), central venous catheter (CVC) use, surgery, renal replacement therapy, diabetes, prolonged mechanical ventilation (MV), severe sepsis and high acute physiology and chronic health evaluation (APACHE) II score. Key diagnostic tool for fungal infection, i.e. blood culture and cultures from various sterile sites of the body, is time-consuming and shows poor sensitivity. Literature regarding use of nonculture-based methods, i.e. beta-glucan assay and polymerase chain reaction (PCR), for diagnosing invasive candidiasis (IC) in ICU population is limited and riddled with lack of standardization and false positive results. It is for these reasons that delayed diagnosis of fungal infections in ICU is a common occurrence. In this setting, several studies have shown a higher mortality associated with delay in empirical appropriate antifungal treatment. Therefore, several investigators have emphasized upon the need of early and appropriate empirical antifungal treatment in high risk patients. Investigators have attempted to develop risk prediction models for identifying high risk groups for IFI. Till date there are only a few studies exploring external validation of these models and in general they have low positive predictive value (PPV) and high negative predictive value (NPV).

EPIDEMIOLOGY

Surveillance and control of pathogens of epidemiologic importance (SCOPE) study conducted in the USA reported *Candida* infection as the fourth most common isolated pathogen accounting for 9% bloodstream infection (BSI). Half to one-third of *Candida* infections occur in ICU patients. A large percentage of ICU patients develop colonization during their stay in ICU. Out of these 5–30% patients develop invasive infection. *Candida albicans* is the most common species responsible for 50–70% cases of candidemia. Non-species account for 30–50% of candidemia cases. Five common species of *Candida* responsible for BSI are *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei*. Rare species causing *Candida* infections are *C. lusitaniae, C. guilliermondii, C. rugosa* (Fig. 1). *Candida* infection is associated with excess attributable mortality of 10–49% and increase in length of hospital stay of 3–30 days.

by mansdocs.com

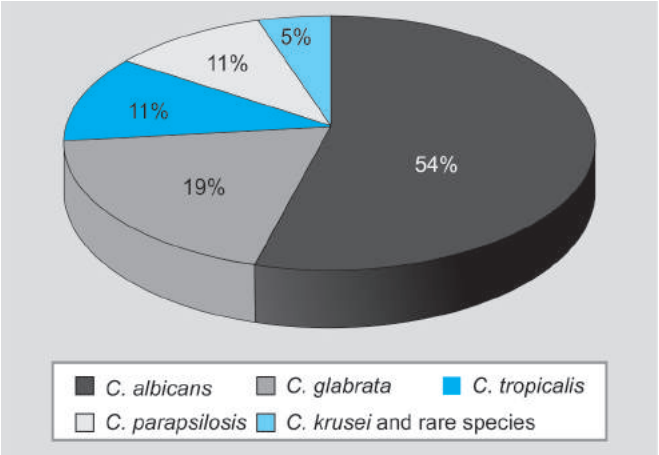


Fig. 1: Species distribution of *Candida* according to SCOPE study conducted in the USA

Candida Albicans

Is the most common species in Europe. However, globally there is a decrease in BSI caused by *C. albicans* and increase in non-albicans related infection. Non-albicans *Candida* species account for more than 50% *Candida* related BSI in Latin and North America. Indian data shows that *C. albicans* is responsible for only 14% *Candida* related BSI while rest are caused by non-albicans. According to SENTRY survey no resistance was reported in *C. albicans* to all five tested antifungal drugs (fluconazole, voriconazole, posaconazole, micafungin and anidulafungin). Though this pattern is changing now as reported in a recently published review where *Candida albicans* was found to be resistant to fluconazole in 1.4% isolates and voriconazole in 1.2% isolates.

Candida Glabrata

A recent study identified six independent factors associated with risk for *C. glabrata* infection including advance age, recent gastrointestinal surgery, solid tumor, recent use of cephalosporins, absence of diabetes mellitus and *Candida* BSI within 7 days of ICU admission. In SENTRY survey *C. glabrata* was found to be resistant to fluconazole in 5.6% cases, voriconazole in 3.5% cases, anidulafungin in 2.4% cases and micafungin in 1.9% cases. Other studies report fluconazole resistance in up to 16% *C. glabrata* isolates.

Candida Parapsilosis

It is an important cause of catheter-related bloodstream infections (CRBSI). Horizontal transmission secondary to poor hand hygiene is well-known with this species. It is responsible for outbreaks of nosocomial candidemias related to CRBSI in neonatal population. It is the second most common species causing *Candida* associated BSI in Europe and Asia Pacific region. According to SENTRY survey, this species was found to be resistant to fluconazole in 5% isolates. It is associated with a crude mortality rate of 30% which is lowest among all *Candida* species.

Candida Tropicalis

It is frequently isolated from patients with hematological malignancy with mucositis and neutropenia. It shows increased virulence in patients with disrupted mucosal barrier. In SENTRY survey, it was found to be resistant to fluconazole and voriconazole in 3.2% and 2.9% isolates respectively.

Candida Krusei

It is responsible for 2–4% of *Candida* associated BSI. Fungemia due to *C. krusei* has crude mortality rate of 59% which is highest among all *Candida* species. Risk factors include recent gastrointestinal surgery, exposure to fluconazole, hematological malignancy. According to SENTRY survey, it was found to be resistant to voriconazole in 2.5% cases while no resistance was reported to anidulafungin, micafungin or posaconazole. Reports of decreased susceptibility to amphotericin B and flucytosine are available.

Aspergillosis

Aspergillus is ubiquitous in soil, air and decaying matter. Common species causing infections in human beings are *A. fumigatus, A. flavus, A. niger, A. terrus*. Out of these *A. fumigatus* is responsible for 50–60% of the infections. Invasive aspergillosis occurs mostly in immunocompromised patients; however, certain groups of patients without known immunosuppression are also showing rise in invasive aspergillosis. They include chronic obstructive pulmonary disease (COPD), cirrhosis, surgical patients, alcoholics, patients suffering from chronic granulomatous infection. Invasive aspergillosis is associated with high mortality rate (up to 80% in disseminated disease).

PATHOGENESIS

Pathogenesis of Invasive Candidiasis

Colonization which is the key factor in pathogenesis is promoted by any condition that decreases immunity as

by mansdocs.com

well as disturbs the normal flora of the body. Factors that decide whether the colonization will convert into infection are:

- Density of colonization
- Host immunity
- *Breach in mucosal barriers*: Like use of invasive catheters, drug-induced mucositis in cancer patients and surgery.

CD4+ T cells play important role in defense against *Candida* infection. T-helper subset Th17 has been identified as critical in preventing *Candida* colonization. Two types of common *Candida* infections occurring in ICU are candidemia following several days of ICU stay and *Candida* peritonitis following complicated abdominal surgery. The disease spectrum caused by *Candida* ranges from transient self-limiting candidemia to multiorgan failure and death. Patient generally presents with persistent fever which does not respond to broad-spectrum antibiotics. Disseminated infection may involve organs like skin, retina, gut, kidneys, heart and central nervous system.

Pathogenesis of Aspergillosis

Aspergillus can give rise to different clinical forms of aspergillosis depending upon the immunological status of the patient. Exposure to *Aspergillus* can lead to allergic reactions in hypersensitive hosts or invasive pulmonary and disseminated disease in immunocompromised individuals. *Aspergillus* spores are acquired from the environment. Role of construction work in the hospital has been implicated in some outbreaks of aspergillosis. Common presentations of invasive aspergillosis include invasive pulmonary aspergillosis, invasive *Aspergillus* sinusitis and cerebral aspergillosis.

DIAGNOSIS

Fungal infections are difficult to diagnose in early phase due to absence of any specific clinical feature and poor sensitivity of the culture-based methods. Moreover, fungal cultures take long to give positive result and blood culture sample size is frequently inadequate due to lack of adherence to the guidelines of equal to or more than 20 mL blood sample. Serological tests and nonculture-based methods are nonspecific and need further studies before they can be used routinely. At one end clinicians find these infections difficult to diagnose while at other end early initiation of antifungal therapy including empirical therapy is associated with improved survival. This issue is further complicated by the fact that routine indiscriminate use of fluconazole is found to be associated with development of azole resistant species. IC is a nosocomial infection which mostly occurs late (median time 22 days) in the course of hospital stay.

RISK PREDICTION MODELS

Many known risk factors, in various combinations, have been studied by several researchers to design risk prediction models to facilitate early empirical antifungal treatment in critically ill patients without severe immunosuppression (Table 1). Following is a brief review of five developmental studies and three well-designed external validation studies available in the literature. Risk of IFI is predicted either on the basis of clinical parameters or microbiological parameters or both.

Prediction on Microbiological Parameters Only

Pittet and coworkers developed colonization index (CI) and corrected colonization index (CCI) in the surgical and neonatal ICUs, by correlating the severity of colonization and infection. A cutoff value of CI more than 0.5 and CCI more than 0.4 could identify all infected patients. They defined colonization as isolation of Candida from three or more samples from same or different sites for two or more consecutive screening days and infection as patient having candidemia or severe Candida species infection requiring use of antifungal therapy. APACHE II and intensity of colonization were found to be independent predictor of Candida infection. These indices have not been validated in nonsurgical patients and are difficult to practice in clinical settings.

Prediction on the Basis of Clinical Parameters (Clinical Prediction Rules)

Many clinical prediction rules have been developed based on clinical parameters.

Many clinical prediction rules (CPRs) have been developed and validated. Dupont et al. identified that four risk factors-cardiovascular failure, upper gastrointestinal tract origin for peritonitis, female gender, and previous antimicrobial therapy were associated with isolation of Candida from peritoneal fluid. Presence of at least three risk factors was associated with a sensitivity of 84% and specificity of 50%. Paphitou rule 2 developed in 2005 for surgical

by mansdocs.com

patients identified ICU stay ≥ 4 days and no antifungal use from day –7 to 3 and any of the following: diabetes or TPN prior to ICU entry or new onset hemodialysis, or broad-spectrum antibiotic use as risk factors for development of candidiasis.

Ostrosky–Zeichner and coworkers 2007 identified antibiotic use or central venous catheter (CVC) use and at least two of additional risk factor (surgery, immunosuppressive use, pancreatitis, TPN, dialysis and steroid use) as risk factors for development of IC in medical & surgical patients. In 2009, they further refined their prediction model and identified mechanical ventilation (MV) for at least 48 hours, antibiotic use, CVC use and at least one of additional risk factors: surgery, immunosuppressive use, pancreatitis, TPN, any dialysis or steroid use as risk factors. The score had a positive predictive value (PPV) of 10%, negative predictive value (NPV) of 97%, with a specificity of 83% and sensitivity of 50%. A validation study suggested the addition of colonization to the clinical risk factors incereased the performance of the CPR.

Nebraska medical center validation study (2011) looked at these scores and showed poor PPV for both Paphitou and Ostrosky rule, but the NPV was high for all the rules (> 98%) and suggested that these CPRs can be helpful in excluding the patient who are not likely to benefit from antifungal therapy rather than selecting the group who will benefit from such therapy.

Prediction on the Basis of Both Microbiological and Clinical Parameters

Some predictive models have included both clinical as well as microbiological parameters. Candida score given by Leon (2006) identified risk factors like surgery on ICU admission, TPN, severe sepsis and multi-site candida colonization as being independently associated with candida infection. For calculating Candida score, each risk factor was given one point except for sepsis which was given two points. A score above 2.5 had sensitivity of 81% and specificity of 74% in predicting proven candidal infection.

DIAGNOSTIC TOOLS

Nonculture-based Methods

Detection of (1,3)-Beta-D-glucan

Glucan is a broad-spectrum test to detect fungal infection. Glucan is a fungal cell wall component of most pathogenic fungi except Zygomycetes and *Cryptococcus*. The test has some limitations. It gives false positive results due to glucan-containing gauze, hemodialysis, Gram-positive bacteremia, immunoglobulins and instruments. A cutoff range of 60 or 80 pg/mL is used. The sensitivity and specificity for 60 pg/mL are 69.9% and 87.1% respectively. If cut-off value of 80 pg/mL is taken, sensitivity and specificity become 64.4% and 92.4% respectively.

Detection of Fungal DNA (PCR Assay)

Polymerase chain reaction-based techniques suffer from high rates of false positive and false negative results. Limited data are available regarding their clinical use.

Antibodies Against Candida albicans Germ Tube

Patients of IC produce antibodies against mannoprotein located on the germ tube cell wall surface of *Candida albicans*. An immunofluorescence assay has been used to detect these antibodies [C. albicans germ tube-specific antibodies (CAGTA)] and commercialized. This test is positive for patients suffering from IC due to *C. albicans*. It can also be positive for non-albicans infections but the titers are generally low. CAGTA titer monitoring helps to monitor resolution of infection also.

Galactomannan Detection

Galactomannan is a cell wall component released during hyphal growth of *Aspergillus*. Chemically, it is a polysaccharide and EIA (sandwich-enzyme immunoassay) is used for its detection in body fluids [mainly bronchoalveolar lavage (BAL)]. It becomes positive generally 5–8 days before onset of clinical disease of invasive aspergillosis. False positive results are frequent in neonatal and pediatric population. This could be because of cross-reacting epitopes of *Bifidobacterium* in neonates and use of piperacillin/tazobactam antibiotic. Galactomannan detection in BAL fluid has a sensitivity and specificity of 88% and 87% respectively.

Combination of Nonculture-based Tests

Various investigators have combined two tests to increase the sensitivity and specificity and PPV:

1. Galactomannan plus (1,3)-beta-D-glucan
2. CAGTA plus (1,3)-beta-D-glucan.

by mansdocs.com

TREATMENT STRATEGIES FOR CANIDIDA INFECTIONS

Treatment for IFI in critically ill patients has evolved from traditional targeted therapy to preventive and early therapeutic strategies. Choice of antifungal agent depends upon following factors:

- Type of therapy chosen (prophylactic, empirical, pre-emptive, targeted)
- Clinical status of the patient (hemodynamically stable/unstable)
- Presence of organ dysfunction in the patient
- Prior antifungal exposure
- Local epidemiological data
- Species identification and antifungal susceptibility.

Prophylaxis

Antifungal prophylaxis is defined as administration of antifungal agents in high risk group of patients without any signs and symptoms of infection to prevent development of such infection.

Three meta-analyses (Cruciani et al. 2005, Shorr et al. 2005, Playford et al. 2006) studied the role of prophylactic antifungal among surgical critically ill patients. Two analyses showed reduction in overall mortality while all three studies showed that antifungal prophylaxis was associated with successful reduction in rate of fungal infections. Though study published by Playford et al. 2006 did not show any epidemiological shift from *C. albicans* to non-albicans after fluconazole prophylaxis, various researchers have shown growing concern regarding this phenomenon.

Prophylaxis for fungal infections is recommended only for high risk groups by most authors. It should not be routinely practiced in all ICU patients. Playford et al. 2006 recommended that prophylaxis should be given to subgroup of population where incidence of IC equal to or more than 10%.

Canadian Guidelines 2010

- Routine prophylaxis is not recommended in all critically ill patients.
- Intensive care unit patients with gastrointestinal perforation should receive injection fluconazole 400 mg once daily (OD) till the intra-abdominal disease has resolved.
- Intensive care unit patients in which the risk of candidiasis or IC is equal to or more than 10% should receive oral fluconazole 400 mg OD till discharge.
- Routine use of antifungal prophylaxis in all severe acute pancreatitis patients is not recommended due to lack of sufficient supportive data.

American Thoracic Society Guidelines 2011

As per American guidelines prophylactic use of antifungal agents remains a controversial issue.

Empirical Therapy

It is therapy given to patients who have clinical signs and symptoms and several risk factors for IFI without any microbiological evidence including species identification and susceptibility study.

Canadian Guidelines 2010

- Empirical therapy may be useful in patients who are identified as high risk based on CPR.
- Injection fluconazole 800 mg loading followed by 400 mg OD is recommended in hemodynamically stable patients.
- Echinocandin (anidulafungin 200 mg loading then 100 mg OD or caspofungin 70 mg loading then 50 mg OD or micafungin 100 mg OD) should be used in hemodynamically unstable patients.
- The duration of therapy should last for at least 14 days.

American Thoracic Society Guidelines 2011

No recommendations for giving empirical antifungal therapy.

Pre-emptive Therapy

In this strategy, therapy is given to high risk group of patients on the basis of positive biomarkers (e.g. positive beta-D-glucan test).

These biomarkers act as surrogate indicator of infection and antifungal therapy is started much before clinical signs and symptoms appear. However, due to high rate of false positivity of these tests and lack of validation studies, pre-emptive therapy presently remains experimental only.

by mansdocs.com

Canadian Guidelines 2010

According to current guidelines, pre-emptive therapy is not recommended in non-neutropenic critically ill patients.

American Thoracic Society Guidelines 2011

No recommendations for giving pre-emptive antifungal therapy.

Targeted Therapy

It is therapy given to patients with clinical signs and symptoms as well as microbiological evidence of IFI.

Canadian Guidelines 2010

- Hemodynamically stable patients with no history of azole exposure should receive injection fluconazole 800 mg loading, followed by 400 mg daily or echinocandin (standard dosing regimen) or amphotericin B deoxycholate 0.5–1 mg/kg/day or lipid formulation of amphotericin B 3 mg/kg/day.
- In case of *C. glabrata* infection fluconazole should be used only if the isolate is documented to be susceptible irrespective of hemodynamic stability.
- For hemodynamically unstable patients with or without azole exposure echinocandin is the drug of choice for all *Candida* species except for *C. parapsilosis*.
- For hemodynamically stable or unstable patients, drug of choice for *C. parapsilosis* is fluconazole or amphotericin B.

American Thoracic Society Guidelines 2011

- In clinically stable patient, fluconazole 400 mg/day or 6 mg/kg/day or echinocandin (standard dosing regimen) should be given.
- In clinically unstable patient, amphotericin B deoxycholate (0.6–1 mg/kg/day) or lipid-based amphotericin B (3–5 mg/kg/day) or echinocandin (standard dosing regimen) or Voriconazole (6 mg/kg/12 hr × 2 doses then 3 mg/kg/12 hr) or high dose fluconazole (800 mg/day or 12 mg/kg/day) or combination regimen with fluconazole (800 mg/day) and amphotericin B (0.6–1 mg/kg/day) should be used.
- Treatment should be continued for 14 days after last positive blood culture.
- All CVCs should be removed. New central venous access should be taken if required.
- All patients should undergo eye examination to rule out ocular dissemination.
- If local epidemiological data report incidence of non-albicans more than 10% then echinocandins should be considered in clinically stable patients and echinocandins or amphotericin B should be considered in unstable patients.

TREATMENT STRATEGIES FOR ASPERGILLUS INFECTIONS

American Thoracic Society Guidelines 2011

- *Primary therapy*: In patients with invasive aspergillosis intravenous voriconazole 6 mg/kg every 12 hr × 2, then 4 mg/kg every 12 hr or intravenous liposomal amphotericin B 3–5 mg/kg till improvement should be given. It should be followed by oral voriconazole (200 mg every 12 hr) or oral itraconazole (400–600 mg/day) until stabilization of all clinical or radiological features of the disease or resolution. Surgical intervention is needed in cases of abscesses, invasion of bone, vitreous disease. It may also be needed in patients with invasive pulmonary aspergillosis when the chemotherapy fails or the lesion impinges over a vessel leading to risk of bleeding. Duration of therapy is generally prolonged up to months and is generally individualized. Therapy can be stopped with clinical and radiological resolution and microbiological clearance.
- *Salvage therapy*: When primary therapy fails, therapy with echinocandins, followed by oral voriconazole or itraconazole is given. A combination of antifungal agents is found to be more effective in such condition.

BASIC PHARMACOLOGY OF ANTIFUNGALS

POLYENES-Prototype Amphotericin B

Chemical preparation: Conventional amphotericin B is a micellar suspension formulation. It is associated with many infusion-related reactions and toxicity. Following three different lipid-based formulations, claiming lesser toxicity and adverse reactions have come up in the market to deal with this issue.

- Liposomal amphotericin B: The drug is encapsulated in phospholipid containing liposomes (LAmB, AmBisome)

by mansdocs.com

- Amphotericin lipid complex: The drug is complexed with phospholipids to form a ribbon-like structure (ABLC, Abelcet)
- Amphotericin B colloidal dispersion (ABCD, Amphotec): The drug is complexed with cholesterol sulfate.

Pharmacodynamics: The best pharmacological predictor of the outcome is ratio of Cmax to MIC, i.e. minimal inhibitory concentration. Drug level is not routinely measured in clinical practice.

Pharmacokinetics: Oral and cutaneous absorption is poor. All preparations are highly protein bound to albumin. Penetration in cerebrospinal fluid (CSF) and vitreous fluid is limited. Intrathecal and intraocular injections are used by some clinicians; however, better drugs are available now. The drug is excreted unchanged via bile and urine. Hepatic and renal failure is not associated with changes in blood concentration. Hemodialysis does not affect the drug level except in hyperlipidemic patients where the drug gets bound to dialysis membrane. Lipid formulations achieve much higher concentration in spleen and liver and lower concentration in kidneys as compared to conventional preparation.

Dose: Conventional amphotericin B 0.6–1 mg/kg, AmBisome 3–5 mg/kg, ABCL 5 mg/kg, ABCD begin with 1 mg/kg, increase up to 3–4 mg/kg.

Side Effects

- Nephrotoxicity due to renal tubular damage (risk can be reduced with pre- and post-hydration)
- Nausea, vomiting, local phlebitis
- Fever, chills and rigor (can be reduced or prevented by slowing the rate of infusion, premedicating with 25 mg hydrocortisone and 25 mg chlorpheniramine)
- Pulmonary reactions like breathlessness and hypoxemia occur when the drug is given along with granulocytes
- Lipid-based preparations are known to have less severe above side effects; however, reversible liver function test abnormalities are known in 25–50% patients treated with AmBisome.

Triazole

Pharmacodynamics: Azoles have species dependent fungistatic or fungicidal action. Primary determinant of efficacy is AUC/MIC ratio.

Individual Agents

Fluconazole: Oral bioavailability is 80–90%. It can be administered without regard to food. Protein binding is only 12%. Kidneys are the main route of elimination. The drug is excreted mainly unchanged in urine. Dose reduction up to 50% is needed in renal failure when creatinine clearance is less than 50 mL/min. After each dialysis session 100% dose replacement is needed.
The drug is well-tolerated except for nausea and vomiting. Rare side effects include hepatitis, cholestasis and hepatic failure. Steven-Johnson syndrome causing fatal exfoliative skin rashes is reported in AIDS patients.

Voriconazole: It has good oral bioavailability. Drug should be preferably given empty stomach as absorption of the drug is reduced after a high fat meal. Protein binding is 60%. It is extensively metabolized by hepatic cytochrome P450 enzyme into inactive metabolites that are excreted in urine. About 2% of the drug is excreted unchanged in urine. Genetic polymorphism exists regarding handling of voriconazole by liver. Some individuals are fast metabolizers while others are slow. Among Asian population, 15–20% population is slow metabolizer and on an average exposed to four-fold higher concentration of the drug. Four hour hemodialysis does not require replacement with extra dose. Sulfobutyl ether beta-cyclodextrin is the carrier used for intravenous preparation which accumulates in patients with moderate to severe renal failure. Oral voriconazole should be preferred in such patients.

Posaconazole: Oral absorption of posaconazole suspension is unpredictable in patients with nausea, diarrhea, and poor intake because it requires food to increase gastric dwell time and drug absorption.

Itraconazole: Drug has incomplete gastrointestinal absorption but can be increased if the drug is given with food. It has high protein binding (up to 99%). Penetration in central nervous system (CNS) is poor but good concentration is achieved in liver, lungs and bone. Drug undergoes extensive metabolism by hepatic cytochrome P450.

Echinocandins

Pharmacodynamics: Main determinant of activity is Cmax/MIC. For optimal fungicidal action peak concentration should be 5–10 times of the MIC. In vitro studies have shown a paradoxical effect of echinocandins. If the drug concentration exceeds a particular level, reduced antifungal activity is observed. The significance of this phenomenon in clinical setting is unknown.

by mansdocs.com

Individual Agents

Anidulafungin: Highly protein bound, poor CSF and vitreous penetration, undergoes nonenzymatic degradation in kidneys. Side effects include diarrhea and hypokalemia. Rarely, deep vein thrombosis and hepatotoxicity can result.

Caspofungin: This drug is fungicidal against *Candida* and fungistatic against *Aspergillus*. It is given only as intravenous preparation. Protein binding is 96%. CNS penetration is poor. It undergoes metabolism in liver and its inactive metabolites are excreted in urine and bile. Hemodialysis does not clear the drug. No dose modification is needed in renal failure but dose reduction is required in patients with moderate hepatic failure. It has minimal side effects like fever, nausea, vomiting, facial swelling, headache and transient rise in liver enzymes.

Micafungin: It is highly protein bound and penetration in vitreous fluid and CSF is poor like other echinocandins. It undergoes nonoxidative metabolism in liver. No dose modification is required in liver or kidney disease.

CASE SCENARIO

A 65-year old female presenting with worsening dyspnea and abdominal pain for 3 days was admitted to the emergency room. On examination the patient was alert and oriented. Her vitals were HR 120 bpm, BP 100/60, SaO_2 92% on oxygen therapy and RR 35 per minute.

The patient had comorbid conditions including type II diabetes, systemic hypertension, mild chronic renal insufficiency for which she was under medical management. The patient was admitted to ICU with an APACHE II score of 18. Invasive arterial and venous pressure monitoring was started. She was intubated and put on MV for respiratory worsening. Physical examination of the abdomen revealed rebound tenderness and X-ray abdomen was positive for air under diaphragm. Baseline investigations showed elevated Total leuckocyte count (TLC) (22,000/mm^3), Serum creatinine 2 mg%, blood urea nitrogen (100 mg%). All routine cultures were sent. Patient was planned for emergency laparotomy which revealed ileal perforation for which resection and repair were done. Antibiotic regimen included piperacillin/tazobactam 4000/500 mg IV four times daily, linezolid 600 mg IV twice daily and clindamycin 600 mg IV four times daily. She received TPN.

On postoperative day four patients developed new onset worsening with high grade fever, tachycardia (130 bpm), rise in TLC (30,000/mm^3) and the need for noradrenalin to maintain systemic pressures. Antibiotics were changed to imipenem 1 g 8 hourly and teicoplanin 400 mg daily and new bacterial cultures were repeated. All previous bacterial cultures were sterile. Patient did not respond to 4 days of therapy and died.

What Could Have Done Wrong?

Possibly patient had IFI because following risk factors were present:

- High APACHE II on admission
- Diabetes
- Surgery
- Central venous catheter
- Use of TPN
- Septic shock
- Broad-spectrum antibiotic use.

What Could Have Been Done?

Diagnostics: *Candida* score could have been done; fungal cultures should also have been done (multifocal colonization should have been ruled out).

Canadian guidelines recommend fluconazole prophylaxis in patients of gastrointestinal (GIT) perforation till the abdominal disease is resolved. Hence fluconazole prophylaxis could have been started at the presentation.

Furthermore empirical antifungal should have been started during secondary postoperative worsening in view of presence of multiple risk factors.

What Would Have Been an Ideal Antifungal Agent?

As the patient was hemodynamically unstable empirical therapy should have been echinocandins.

CONCLUSION

Many diverse clinical conditions have been found to be significantly associated with risk of IFI. Based on these risk factors risk prediction models have been designed. Models which include clinical as well as microbiological parameters for identifying high risk group perform better as compared to models using clinical parameters alone. These models should be judiciously used for identifying high risk group and early initiation of antifungal therapy. Waiting for the positive culture report can result in delay in therapy and increased morbidity and mortality. Antifungal agent should be selected after considering the local epidemiological data and clinical condition of the patient that includes hemodynamic status and organ dysfunction.

by mansdocs.com

KEY POINTS

- Fungal infections are rising globally.
- There is a trend toward increase in infections caused by *Candida* non-albicans.
- Risk factor identification and early initiation of prophylactic or empirical antifungal therapy are key steps in management of critically ill patients.
- Broad-spectrum antifungal agents should be used for all hemodynamically unstable patients suspected of IFI.

BIBLIOGRAPHY

1. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. Ann Intensive Care. 2011;1:37.
2. León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006;34(3):730-7.
3. Ostrosky-Zeichner L, Pappas PG, Shoham S, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. Mycoses. 2011;54(1):46-51.
4. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol. 2005;43(3):235-43.
5. Parkins MD, Sabuda DM, Elsayed S, et al. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive Candida species infections. J Antimicrob Chemother. 2007;60(3):613-8.
6. Pittet D, Monod M, Suter PM, et al. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg. 1994;220(6):751-8.
7. Playford EG, Lipman J, Kabir M, et al. Assessment of clinical risk predictive rules for invasive candidiasis in a prospective multicentre cohort of ICU patients. Intensive Care Med. 2009;35(12):2141-5.

by mansdocs.com

CHAPTER

52

Febrile Neutropenia

Rajesh Pande

INTRODUCTION

About half of febrile neutropenic patients have a documented or occult infection. Clinical presentation in febrile neutropenics may present like a new onset infection, e.g. the patient might present with cough with expectoration, fever, tachycardia, and hypotension with tachypnea and desaturation. Chest examination may reveal signs of pneumonia like absent air entry right base, bilateral crepitations. The arterial blood gas may show high anion gap metabolic acidosis, hypoxemia and rising lactates.

The investigations may show anemia, leukopenia with very low neutrophil count and thrombocytopenia. Infection markers like C-reactive protein and procalcitonin may be raised. The blood, urine and lower respiratory tract samples may show a positive growth. Ultrasound and 2D echocardiography may reveal some abnormality or dysfunction.

AN ILLUSTRATIVE CASE

A 35-year-old woman operated for carcinoma ovary, received six cycles of chemotherapy followed by hormonal therapy later. There is recurrence of the disease. The patient is running with fever, and the X-ray shows right-sided pneumonia (Fig. 1) and she is severely neutropenic. She was prescribed combination antibiotics, antifungals, and a colony-stimulating agent. This illustrates how sometimes febrile neutropenia can present, but most times it presents in a subtle way making diagnosis difficult.

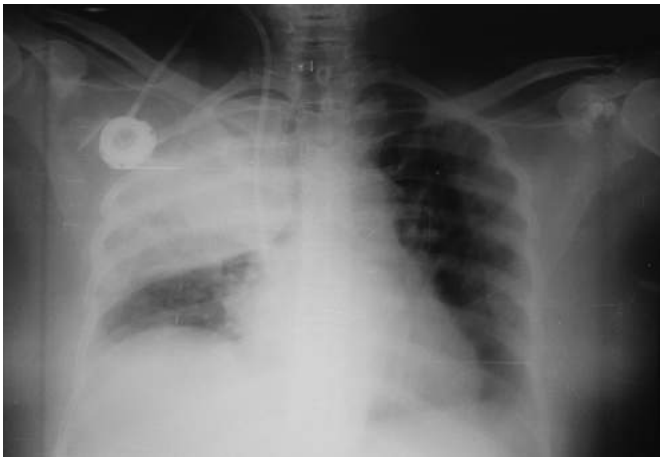


Fig. 1: X-ray shows right-sided pneumonia

DEFINITION OF FEBRILE NEUTROPENIA

An oral temperature is more than 38.5°C or two consecutive readings of more than 38.0°C for 2 hours and an absolute neutrophil count less than 0.5×10^9/L, or expected to fall below 0.5×10^9/L.

These patients may require urgent blood testing to assess bone marrow, renal and liver function, coagulation screen, C-reactive protein, blood cultures (minimum of two sets) including cultures from indwelling intravenous (IV) catheter, urinalysis and culture, sputum microscopy and culture, stool microscopy and culture, skin lesion (aspirate/biopsy/swab), chest radiograph and higher imaging like computed tomography (CT) scan as required.

by mansdocs.com

Table 1: MASCC scoring system.

Characteristic	*Score*
• *Burden of illness*: No or mild symptoms	5
• *Burden of illness*: Moderate symptoms	3
• *Burden of illness*: Severe symptoms	0
• No hypotension (systolic BP > 90 mm Hg)	5
• No chronic obstructive pulmonary disease	4
• Solid tumor/lymphoma with no previous fungal infection	4
• No dehydration	3
• Outpatient status (at onset of fever)	3
• Age < 60 years	2

Further investigations may be required in profound/prolonged neutropenics/following allografts and include high-resolution chest CT (if pyrexial despite 72 hours of appropriate antibiotics), bronchoalveolar lavage.

There are standard-risk assessments like Talcott classification of risk groups and MASCC group—Multinational Association for Supportive Care in Cancer. Both the scores take serious medical complications as endpoint for risk prediction. Risk assessment in febrile neutropenia can help one decide "Whether to admit or not?" and also helps one decide between oral and IV antibiotics.

These patients can be classified clinically into low- and high-risk groups:

Low-risk patients include:

- Out patient department (OPD) conventional chemotherapy for solid tumors
- Normal chest X-ray
- Hemodynamically stable
- Normal liver and kidney functions
- Normal mental status
- Expected duration of neutropenia less than 7 days
- Early evidence of marrow recovery.

The problems with Talcott classification include:

- Low sensitivity 30%
- High misclassifications
- Patients who do not have complications are not identified.

MASCC classification (Table 1): It is based on history, age, outpatient status, clinical status at presentation and comorbidities. If the score is less than 20, it is considered low risk.

Common Causative Bacterial Pathogens Implicated in Febrile Neutropenia

The causative agents are listed in Table 2.

Table 2: Common bacterial pathogens in neutropenic patients.

Common Gram-positive pathogens
• Coagulase-negative staphylococci
• *Staphylococcus aureus*, including methicillin-resistant strains
• *Enterococcus* species, including vancomycin-resistant strains
• Viridans group streptococci
• *Streptococcus pneumoniae*
• *Streptococcus pyogenes*
Common Gram-negative pathogens
• *Escherichia coli*
• *Klebsiella* species
• *Enterobacter* species
• *Pseudomonas aeruginosa*
• *Citrobacter* species
• *Acinetobacter* species
• *Stenotrophomonas maltophilia*

MANAGEMENT OF FEBRILE NEUTROPENIA

Initial Management Approach

The initial management approach in febrile neutropenic is outlined in Flowcharts 1 and 2.

Indications for Adding a Gram-positive Antibiotic

- Evidence of severe sepsis or hemodynamic instability.
- Chest X-ray showing pneumonia.
- Positive blood culture for Gram-positive cocci (GPC), identification, sensitivity pending.
- Serious line related sepsis suspected.
- Skin or soft tissue infection at any site.

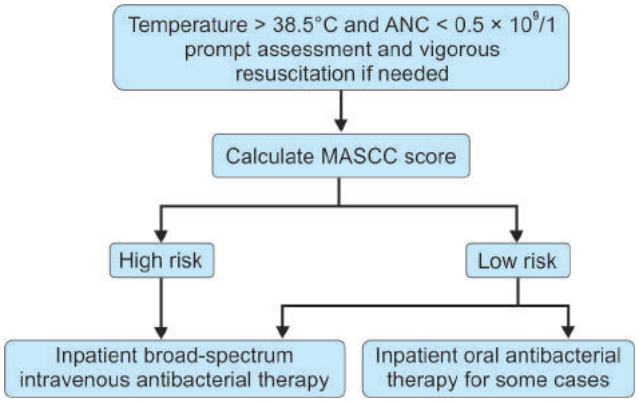
Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* or penicillin-resistant *Streptococcus pneumoniae*. Severe mucositis, if *fluoroquinolone* prophylaxis has been given, ceftazidime is used as empirical therapy.

Management Approach to Patients Who Remain Febrile After 24–48 Hours of Antibiotic Therapy

- Persistent fever more than 39°C and chills, and rigor 24–48 hours after starting therapy.
- Relapse of fever more than 38°C.
- Progression of sepsis syndrome.

by mansdocs.com

Flowchart 1: Management of febrile neutropenia.



- Development of disseminated intravascular coagulation, acute respiratory distress syndrome, and multiple organ failure.
- Appearance of a new infection.

AN APPROACH TO FEBRILE NEUTROPENIC PATIENTS

An algorithm shows an approach to febrile neutropenic patients (Flowcharts 2 and 3).

Neutropenics who remain febrile after 24–48 hours need further evaluation.

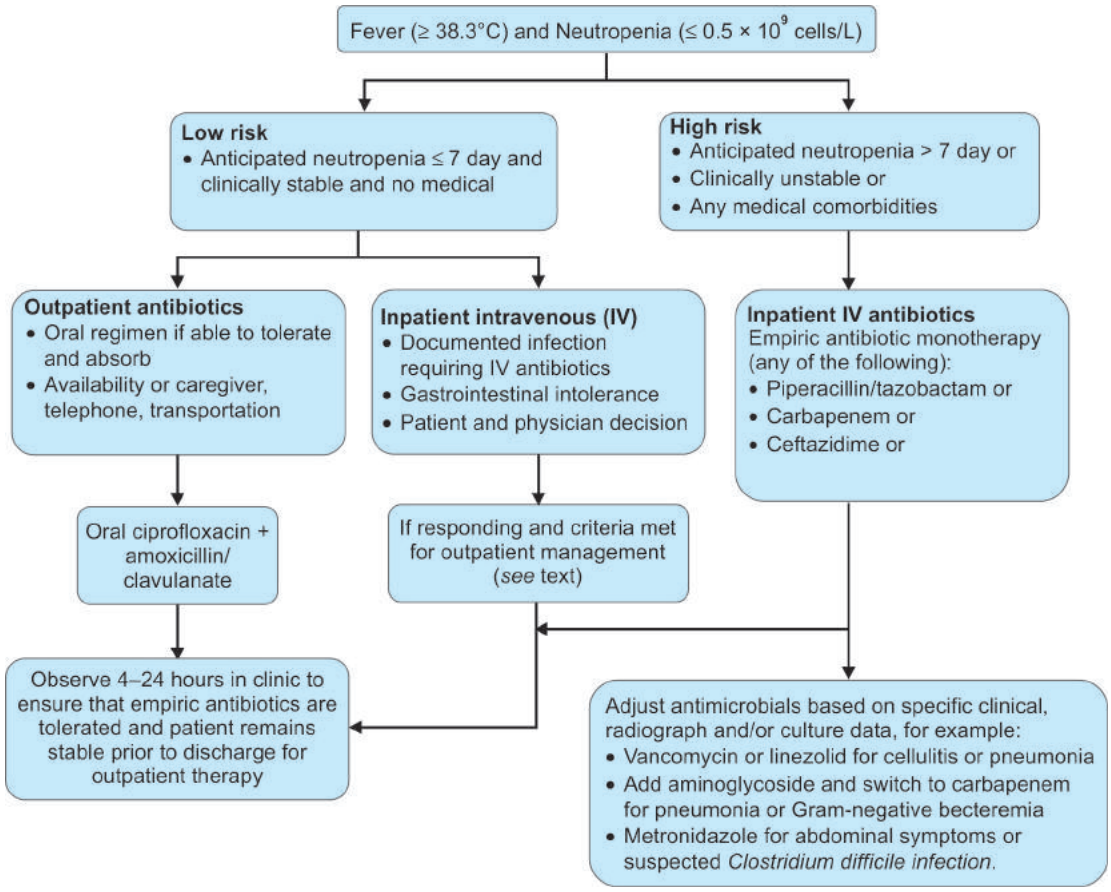
Consider Alternate Causes of Fever

- Drug-resistant organism.
- Drug reactions.
- Infusion of blood products.
- Graft versus host disease.

Special Patient Groups Like Bone Marrow Transplant may Require More Extensive Evaluation

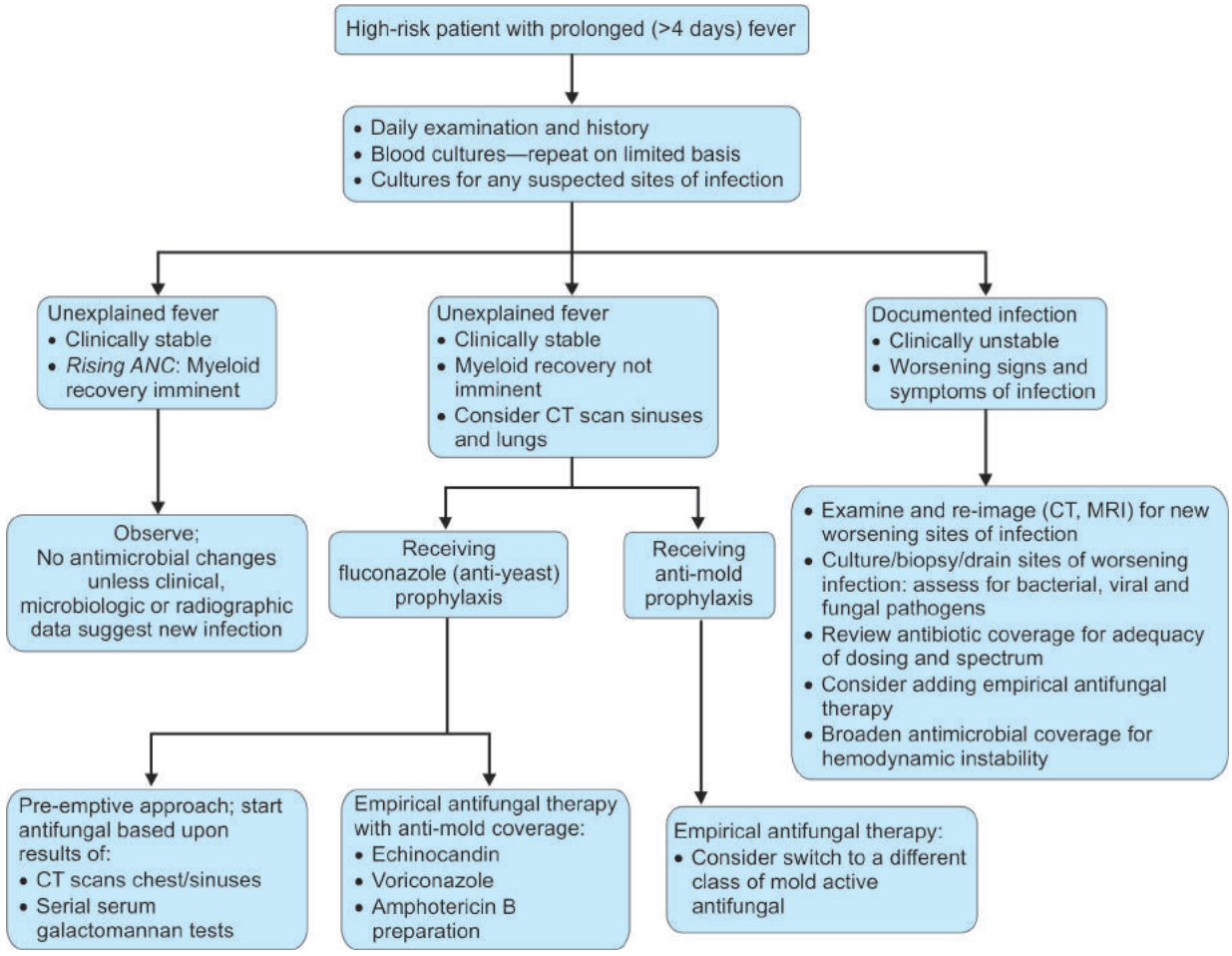
- Bacteremia/herpes simplex virus/candidiasis/invasive fungal infection.

Flowchart 2: An approach to febrile neutropenic patients.



by mansdocs.com

Flowchart 3: An approach to high-risk patients.



- *Post-engraftment up to 100 days*: Gram-positive cocci, Gram-negative bacteria/fungal/Cytomegalovirus (CMV)/porcine circovirus/other viruses
- *From 100 days to 1 year*: Varicella zoster virus/encapsulated bacteria.

Evaluation in Solid Organ Recipients

- Ventilator-associated pneumonia/line infection/wound infection/urinary tract infections.
- *About 2–6 months postoperation*: Wide range; all infections can occur.
- *After 6 months*: Same risk of bacterial infection as a minimally immunosuppressed patient in the community.
- Post-transplant screening:
  - CMV by polymerase chain reaction (PCR)
  - Candida and aspergillosis by antigen test.

The management approach is outlined in Flowchart 3.

Duration of Antibiotic Therapy

- No fever and neutrophil more than or equal to 500 cells/μL, no source of infection—stop A/B when afebrile for more than 48 hours.
- No fever and neutrophil less than 500 cells/μL—by day 7, patient looks healthy, it is low risk. Stop A/B when afebrile for 5–7 days.
- If high risk—continue for 14 days.
- *Fever and neutrophil more than or equal to 500 cells/μL*: Consider stopping 4–5 days after neutrophil less than 500 cells/μL.
- *Fever and neutrophil less than 500 cells/μL*: Continue for 2 weeks; consider fungal superinfection.

by mansdocs.com

SUMMARY

The use of empiric antibiotic therapy in febrile, neutropenic cancer patients has now become well resulting in drastic reduction in high mortality seen until the 70s. For better management, it is important to understand the nature of microorganisms responsible for infection, and a careful evaluation, risk assessment to guide therapy and appropriate use of antimicrobials. The signs and symptoms of infection in febrile neutropenic may not always be very obvious necessitating an organized approach to the fever. Information about resistant microorganisms, their resistant pattern in the hospital may help in deciding about empiric antimicrobial therapy.

BIBLIOGRAPHY

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):e56-93.
2. Kannangara S. Management of febrile neutropenia. Community Oncology. 2006;3:585-91.

by mansdocs.com

CHAPTER

53

Fever in the ICU

Rajesh Pande

INTRODUCTION

Fever in the intensive care unit (ICU) could be infectious, noninfectious or mixed origin, and confirmation of source is difficult. ICU fever remains a diagnostic dilemma—whether to treat or not to treat. Thirty percent patients become febrile during hospitalizations and up to 90% critically ill patients with severe sepsis experience fever during ICU stay. ICU patients will generally present a newly elevated temperature at some point during their stay. A prudent, cost-effective assessment is necessary.

The goal for the treatment of a new temperature elevation in a previously afebrile, critically ill patient in whom the source of fever is not obvious merits a detailed evaluation of the patients medical history and a careful physical examination before the order of any laboratory or imaging procedure or before the administration of any drug: the goal is to promote the rational consumption of different resources and the efficient evaluation of the new event. [American College of Critical Care Medicine (ACCM) and Infectious Disease Society of America (IDSA)].

DEFINITIONS

Mean body temperature: 36.8°C (98.2°F) (35.6–38.0°C/96–100.8°F). *Fever is defined as*: Core temperature more than 38°C (100.4°F) or two consecutive measurements show temperature more than 38.3°C (101.0 °F). In neutropenic patients, a single oral temperature more than 38°C for more than one hour suggests fever.

PHYSIOLOGY

Exogenous stimuli like infection, inflammation, autoimmune disease, vaso-occlusive diseases cause release endogenous pyrogens like IL-1, TNF-α, IL-6 and interferon a, which cross blood-brain barrier and bind to receptors in anterior hypothalamus leading to the production of arachidonic acid metabolites (prostaglandin E2 and thromboxane A2) resulting in upregulation of thermostatic set point. The brain sends signal to the body to generate heat, reduce heat loss and to increase body temperature to match the upregulated thermostatic point.

BENEFICIAL EFFECTS OF FEVER

A rise in body temperature is associated with enhanced resistance to infection in mammalian models. A positive correlation seen between maximum temperature on bacteremia day and survival or between a temperature more than 38°C and survival in spontaneous bacterial peritonitis in experimental studies.

DELETERIOUS EFFECTS OF FEVER

In patients with cardiorespiratory diseases, it causes increase in cardiac output, CO_2 production and energy expenditure. It causes exacerbation of injuries in head injury and cerebro-vascular accident (CVA) patients. Fever results in increased oxygen consumption (13% rise for each 1°C rise in temperature), increase in heart rate, cardiac output and catecholamine production.

by mansdocs.com

NONINFECTIOUS CAUSES OF FEVER

- *Central nervous system (CNS)*: Subarachnoid hemorrhage, intracerebral hemorrhage, infarction.
- *Cardiac:* Myocardial infarction, pericarditis.
- *Pulmonary*: Atelectasis, PE, fibro-proliferative phase of acute respiratory distress syndrome (ARDS).
- *Hepatobiliary and gastrointestinal tract (GIT)*: Acalculous cholecystitis, acute pancreatitis, active Crohn's disease, toxic megacolon, and alcoholic hepatitis.
- *Rheumatologic syndromes*: Vasculitis, systemic lupus erythematosis (SLE), rheumatic arthritis (RA), Goodpasture's syndrome.
- *Endocrine*: Hyperthyroidism, adrenal insufficiency, and pheochromocytoma.

OTHER NONINFECTIOUS CAUSES OF FEVER

- Drug fever
- Transfusion reactions
- Neoplasms
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Opioid withdrawal syndrome
- Alcohol withdrawal syndrome
- Devitalized tissue secondary to trauma
- Hematoma.

INFECTIOUS CAUSES OF FEVER

- *CNS*: Meningitis, encephalitis, brain abscess, and epidural abscess.
- *Head and neck*: Acute suppurative parotitis, acute sinusitis, acute suppurative otitis media (ASOM), para and retropharyngeal abscesses.
- *CVS*: Endocarditis, catheter-related infection.
- *Pulmonary and mediastinal*: Pneumonia, empyema, and mediastinitis.
- *Hepatobiliary and GIT*: Appendicitis, diverticulitis, peritonitis, intraperitoneal abscess, perirectal abscess, infected pancreatitis, acute cholecystitis, cholangitis, hepatic abscesses, and acute viral hepatitis.
- *Genitourinary*: Bacterial or fungal cystitis, pyelonephritis, perinephric abscess, tubo-ovarian mass, endometritis, and prostatitis.
- *Breast*: Mastitis, abscess.
- *Cutaneous*: Cellulitis, suppurative wound infection, necrotizing fasciitis, bacterial myositis, and herpes zoster.
- *Osseous*: Osteomyelitis.

DRUG FEVERS

They result from drug reactions. The incidence is 3–7%. The temperature ranges from 38–40°C. It is Difficult diagnosis usually by exclusion. Concomitant maculopapular rash may make the diagnosis easier (only in 5–10% cases). The time between initiation of a drug and drug fever is 21 days (median 8 days). The fever generally resolves within 72 hours of stopping the offending drug. The high-risk agents in drug fevers are:

- β-lactam antibiotics
- *Antiepileptic drugs*: Phenytoin
- *Antiarrhythmic*: Quinidine, procainamide
- *Antihypertensive*: Alpha-methyldopa
- Diuretics
- Stool softeners
- *Antibiotics with lower risk*: Clindamycin, vancomycin, aztreonam, imipenem, aminoglycosides, quinolones, erythromycin, doxycycline, and chloramphenicol.

POSTOPERATIVE FEVER

It is common within first 72 hours after surgery. However, one should be cautious to look for infections if fever persists beyond 72 hours, it could be due to pneumonia, wound infection and urinary tract infection (UTI). The surgical wounds/incision sites should be examined for any sign of infection. Keep a suspicion of pulmonary embolism, deep venous thrombosis and superficial thrombophlebitis.

APPROACH TO FEVER IN ICU

Key elements in evaluation of new-onset fever in ICU:

- History and physical examination
- Look at wounds, surgical incision sites, vascular access, and pressure ulcers
- Obtain/review chest X-ray, look for new infiltrates or effusions
- *Appropriate lab studies*: Cultures, WBC and PBS
- Remove central venous catheters that are more than 96 hours old. Send tip for semiquantitative culture
- Send stool sample in patients on antibiotics for more than 3 days for *Clostridium difficile* toxin

by mansdocs.com

- Diagnostic thoracocentesis, paracentesis and lumbar puncture may be done as per the need
- Ultrasound/CT may be used to identify the source.

NEW FEVER IN ICU

The patients may not necessarily be febrile and may be euthermic or hypothermic with life-threatening infection:

- Elderly
- Open abdominal wounds
- Large burns
- Patients on ECMO, CRRT
- CHF
- End-stage liver disease, CRF
- Patients on anti-inflammatory or antipyretic drugs.

Symptoms and signs in the absence of fever, which mandate a comprehensive search for infection and aggressive, immediate empirical therapy: Unexplained hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, immature neutrophils (i.e. bands) of 10%, or thrombocytopenia.

RECOMMENDATIONS FOR MEASURING TEMPERATURE

- *Accurate and reliable method based on the clinical circumstances*:
  - Do not use the following in the ICU (level 2)-Axillary measurements, temporal artery estimates, and chemical dot thermometers
  - Avoid rectal thermometers in neutropenic patients (level 2).
- Temperature measuring device should be maintained and calibrated appropriately, using the manufacturer's guidelines as a reference (level 2).
- *Most accurate methods are*:
  - Pulmonary artery thermistor
  - Urinary bladder catheter thermistor
  - Esophageal probe
  - Rectal probe.
- *Other acceptable methods in order of accuracy:*
  - Oral probe
  - Infrared ear thermometry.
- *Other less desirable methods*
  - Temporal artery thermometer
  - Axillary thermometer
  - Chemical dot.
- *Diagnostic evaluation*:
  - Blood culture
  - Evaluation of pulmonary infection
  - Stool evaluation in diarrhea
  - Evaluation of urinary tract
  - Evaluation of nervous system
  - Evaluation of sinuses
  - Evaluation of surgical fever
  - Biomarkers—procalcitonin and endotoxin assay.

RECOMMENDATIONS FOR OBTAINING BLOOD CULTURES

- *Culture number*:
  - Obtain 3–4 blood cultures within the first 24 hours of the onset of fever
  - Obtain first cultures before the initiation of antimicrobial therapy. They should be drawn consecutively or simultaneously
  - For endovascular infection—separate venipunctures by timed intervals can be drawn to demonstrate continuous bacteremia (level 2).
- *Additional blood cultures to be drawn only*:
  - Clinical suspicion of continuing or recurrent bacteremia or fungemia
  - Or for test of cure
  - 48–96 hours after initiation of appropriate therapy for bacteremia/fungemia
  - Additional cultures should always be paired (level 2).
- *For patients—without an indwelling vascular catheter*:
  - At least two blood cultures using strict aseptic technique from peripheral sites by separate venipunctures after appropriate disinfection of the skin (level 2).
- *For cutaneous disinfection*:
  - Two percent chlorhexidine gluconate in 70% isopropyl alcohol is the preferred skin antiseptic
  - Tincture of iodine is equally effective
  - Both require -30 seconds of drying time before the culture procedure
  - Povidone iodine is an acceptable alternative; it must be allowed to dry for 2 minutes (level 1).
- The injection port of the blood culture bottles should be wiped with 70–90% alcohol before injecting the blood sample into the bottle to reduce the risk of introduced contamination (level 3).

by mansdocs.com

- *If the patient has an intravascular catheter*:
  - One blood culture should be drawn by venipuncture
  - At least one culture should be drawn through an intravascular catheter
  - Only intravascular catheters yield slightly less precise information than information (level 2).
- Label the blood culture with the exact time, date, and anatomic site from which it was taken (level 2).
- Draw 20–30 mL of blood per culture (level 2).
- Paired blood cultures more useful information. Single blood cultures are recommended, only in neonates (level 2).
- Additional blood cultures should be ordered based on clinical suspicion of continuous or recurrent bacteremia or fungemia (level 2).

Recommendations for Management of Intravascular Catheters

- Examine the patient at least daily for inflammation or purulence at the exit site along the tunnel. Assess the patient for signs of venous thrombosis or evidence of embolic phenomena (level 2).
- Any expressed purulence from the insertion site should be Gram stained and cultured (level 2).
- If evidence of infection is present—tunnel infection embolic phenomenon, vascular compromise, or septic shock—the catheter should be removed and cultured, and a new catheter inserted at a different site (level 2).
- *Catheter-related sepsis*:
  - *Short-term temporary catheters*: The suspect catheter be removed, and a catheter segment cultured. Positive blood cultures should be obtained as well
    - 5- to 7-cm intracutaneous segment should be cultured to document the source of bacteremia; the tip should be cultured.
  - *Longer central venous catheters*: The intracutaneous segment and tip should be cultured
  - With pulmonary artery catheters, the introducer and the pulmonary artery catheter should be cultured (level 1).
- *At least two blood cultures should be obtained*:
  - Peripherally by venipuncture from the suspected catheter (level 1)
  - If a quantitative culture system is available, it should be used to diagnose the catheter as the source of bacteremia/fungemia, or
  - Differential time to positivity can be used if both blood cultures are positive for the same organism
  - The distal port is the port to draw cultures.
- If short-term, uncuffed central venous catheters suspected as source, it is usually more efficient to remove the existing catheter and replace it than to draw quantitative cultures (level 2).
- Culture only those catheters suspected of being the source of infection (level 2).
- It is not necessary to routinely culture infusate specimens as part of the evaluation for catheter-related infections, unless there is clinical suspicion for infected infusate or blood products (level 2).

RECOMMENDATIONS FOR EVALUATION OF PULMONARY INFECTIONS

- If an immuno-compromised febrile patient is suspected of having lower respiratory tract infection, an upright portable anteroposterior/posteroanterior/lateral chest X-ray or CT scans provide good information on opportunistic infections.
- Before initiation of or change in antibiotics, send one sample of lower respiratory tract secretions for direct examination and culture.
  - Sample—Expectorated sputum, induced sputum, tracheal secretions, bronchoscopic or nonbronchoscopic alveolar lavage (level 2).

IF PNEUMONIA IS DOCUMENTED

- Diagnostic modalities include bronchoscopy. The invasive diagnostic approaches should be considered based on an individual basis and the availability of local expertise (level 2).
- Transport—Respiratory secretions for microbiological evaluation should be processed in 2 hours (level 2).
- Evaluation includes Gram-negative stain and cultured for aerobic and facultative bacteria. Additional stains, rapid tests, cultures, and other tests should be performed as epidemiologically appropriate (level 2).

RECOMMENDATIONS FOR CULTURES IN PULMONARY INFECTIONS

- Quantitative cultures can provide useful information in certain patient populations when assessed in experienced laboratories. The drawbacks are that quantitative cultures have not yet been sufficiently standardized (level 2).

by mansdocs.com

- Pleural fluid should be obtained with ultrasound guidance for Gram-negative stain and routine culture if there is an adjacent infiltrate or suspicion of infection and the fluid can be safely aspirated (level 2).

Recommendations for Evaluation of Gastrointestinal Tract Stool Evaluation in Febrile ICU Patient

- If more than two stools per day conform to the risk of *C. difficile*
  - Send one stool sample for *C. difficile* common antigen → EIA (glutamate dehydrogenase) for toxin A and B, tissue culture assay (level 2)
  - If the first specimen for *C. difficile* is negative and testing is performed by an EIA method
    - Send an additional sample for *C difficile* EIA evaluation
    - A second specimen is not necessary if the common antigen test was negative (level 2)
    - If severe illness is present and rapid tests for *C. difficile* are negative or unavailable, consider flexible sigmoidoscopy (level 3).
  - If severe illness is present consider empirical therapy with vancomycin awaiting diagnostic studies
  - Empirical therapy is not generally recommended if two stool evaluations are negative using a reliable assay
  - The empirical use, especially vancomycin is discouraged because of the risk of producing resistant pathogens (level 2).
- Stool cultures for other enteric pathogens are indicated in patients with diarrhea or human immunodeficiency virus (HIV) infected.
  - Send stool cultures for other enteric pathogens and examine for ova and parasites only if it is epidemiologically appropriate and for evaluating an immunocompromised host (level 2).
- Test stool for Norovirus if the clinical and epidemiologic setting is appropriate and the test is available.
- Obtain consultation with infection control and public health authorities (level 3).

RECOMMENDATIONS FOR EVALUATION OF THE URINARY TRACT

- For patients at high risk for urinary tract infection clinical evaluation are symptomatic. Laboratory evaluation is necessary.
- Obtain urine for microscopic examination, Gram-negative stain, and culture (level 2).
- Kidney transplant granulocytopenic patients, patients with recent urologic surgery or obstruction
- Collection → urine collected from the sampling port of the catheter and not from the drainage bag (level 2)
- *Transportation of sample*:
  - Urine should be transported to the laboratory and processed within 1 hour to avoid bacterial multiplication.
  - If it requires more than 1 hour, the specimen should be refrigerated. (a preservative level 2).
- Cultures from catheterized patients showing –10^3 cfu/mL
  - *Bacteriuria or candiduria*: Neither higher counts nor the presence of pyuria alone are of much value in determining if the catheter-associated bacteriuria or candiduria is the cause of a patient's fever; in most cases, it is not the cause of fever (level 1).
- Gram stains of centrifuged urine will reliably show the infecting organisms and can aid in the selection of anti-infective therapy if catheter-associated urosepsis is suspected (level 1)
- Rapid dipstick tests are not recommended for patients with urinary catheters in the analysis of possible catheter-associated infection (level 1).

RECOMMENDATIONS FOR EVALUATION OF CENTRAL NERVOUS SYSTEM

- *Lumbar puncture*: If altered consciousness or focal neurologic signs are unexplained, in patients with a new fever unless contraindication to lumbar puncture (level 3). If there is mass lesion or obstructive hydrocephalus, non contrast computed tomography (NCCT) of the head should be done.
- For a patient with a new fever and new focal neurologic findings optimal diagnostic approach (level 2) an imaging study is usually required before lumbar puncture for disease above the foramen magnum.
- Neurology/neurosurgery consultation is required, if a mass is present.
- In febrile patients with an intracranial device, cerebrospinal fluid (CSF) should be obtained for analysis from the CSF reservoir. If CSF flow to the subarachnoid space is obstructed, it may also be prudent to obtain CSF from the lumbar space (level 3).
- In patients with ventriculostomies who develop stupor or signs of meningitis, the catheter should be removed and the tip cultured (level 3).

by mansdocs.com

- CSF should be evaluated by Gram-negative stain and culture, glucose, protein, and cell count with differential.
- Additional tests for tuberculosis, viral and fungal disease, neoplasia etc., should be dictated by clinical situation (Level 2).

RECOMMENDATIONS FOR EVALUATION OF THE SINUSES

- If clinical evaluation suggests that sinusitis may be a cause of fever, a CT scan of the facial sinuses should be obtained (level 2).
- If the patient has not responded to empirical therapy, puncture and aspiration of the involved sinuses under antiseptic conditions should be performed (level 2).
- Aspirated fluid should be sent for Gram-negative stain and culture for aerobic and anaerobic bacteria and fungi to determine the causative pathogen and its antimicrobial susceptibility (level 1).

RECOMMENDATIONS FOR EVALUATION OF FEVER WITHIN 72 HOURS OF SURGERY

- A chest radiograph is not mandatory during the initial 72 hours postoperatively if fever is the only indication (level 3).
- A urinalysis and culture are not mandatory during the initial 72 hours postoperatively if fever is the only indication.
- Urinalysis and culture should be performed for those febrile patients having indwelling bladder catheters for 72 hours (level 3).
- Surgical wounds should be examined daily for infection. They should not be cultured if there is no symptom or sign suggesting infection (level 2).
- Suspect deep venous thrombosis, superficial thrombophlebitis and pulmonary embolism, in patients who are sedentary, have lower limb immobility, or a malignant neoplasm, or on an oral contraceptive level 2).

RECOMMENDATIONS FOR EVALUATION OF SURGICAL SITE INFECTION

- Examine the surgical incision at least once daily for erythema, purulence, tenderness as part of the fever evaluation (level 2).
- If there is suspicion of infection, the incision should be opened and cultured (level 2).
- Gram-negative stain and cultures should be obtained from any expressed purulence obtained from levels within the incision consistent with a deep incisional or organ/space surgical site infection. Tissue biopsies or aspirates are preferable to swabs (level 3).
- Drainage from superficial surgical site infections may not require Gram-negative stain and culture. Incision, drainage and local care may be sufficient and treatment with antibiotic therapy may not be required. Superficial swab cultures are likely to be contaminated with commensal skin flora and are not recommended (level 2).
- Standard guidelines should be used to define burn wound infection.

RECOMMENDATIONS FOR USING BIOMARKERS TO DETERMINE THE CAUSE OF FEVER

- Biomarkers as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis are serum procalcitonin levels and endotoxin activity assay: Endotoxin activity assay uses antibody to the conserved lipid A component of endotoxin to form an antibody antigen complex capable of stimulating a detectable host neutrophil respiratory burst in an ex vivo assay.
- Sensitive Serum Procalcitonin Assay is approved for the early detection of bacterial infections and sepsis in patients during the first day of ICU admission. A rise in procalcitonin to 0.5 ng/mL occurs within 2–3 hours of onset. A value of 0.6–2.0 ng/mL is suggestive of systemic inflammatory response syndrome (SIRS), 2–10 ng/mL of severe sepsis, and 10 ng/mL of septic shock. It is not elevated in: viral infections, recent surgery, and chronic inflammatory states.

BIBLIOGRAPHY

1. O'Grady NP, Barie SP, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med. 2008;36(4):1330-49.

by mansdocs.com

CHAPTER

54

Cytomegalovirus Infection in Critically Ill Patients

Armin Ahmed, Afzal Azim, Mohan Gurjar, AK Baronia

INTRODUCTION

Reactivation of latent cytomegalovirus (CMV) infection in transplant recipients, cancer and human immunodeficiency virus patients, is a well-known phenomenon and is linked with suppression of cell-mediated immunity. The role of such infections in immunocompetent critically ill patients remains poorly defined. These patients are exposed to multiple broad-spectrum antibiotics and invasive equipments, making them a potential candidate for nosocomial infections. Most of the nosocomial infections are thought to be bacterial or fungal in origin, but viral infections may represent a hidden unrecognized burden.

Cytomegalovirus is widely distributed around the globe. Infection is more common in less developed countries with poor hygienic conditions. Spread of infection occurs with prolonged intimate contact with the infected individual. Most infected patients do not show any symptom and diagnosis can be made only by measuring the antibody titers. Seroprevalence rate increases steadily with age. It is reported to be 65% among 40–50 years old and increases to 91% in those aged 80 years or above. Once infected, the virus remains in the body throughout the life. Asymptomatic shedding can occur in infected immunocompetent individuals, but cell-mediated immunity prevents the development of overt clinical disease.

In critically ill patients reactivation of the latent infection is mainly considered to be the cause of CMV disease, though acquisition of primary infection is also possible. Osawa et al. A systemic review evaluating the rate of CMV infections on the basis of viral cultures, antigenemia or DNAemia by polymerase chain reaction in critically ill immunocompetent patients revealed a 0-36% CMV infection rate, with a median of 25%. This rate was even higher in seropositive patients (13–56%). Specimens used in various studies were urine, blood and respiratory secretions. Out of total 13 studies analyzed, some reported an incidence ranging from 25% to 35%, whereas others found very low or no CMV infection. These discrepancies may be explained by differences in study design, patient populations, methods and delay of CMV infection diagnosis. Studies which monitored infection only at the time of intensive care unit (ICU) admission showed lower rates of CMV infection as compared to studies in which monitoring was done weekly. Therefore, frequency of monitoring can influence the rate of CMV infection reported in a study.

RISK FACTORS

Risk factors for reactivation include sepsis, burns, prolonged mechanical ventilation, prolonged ICU stay and multiple transfusions. Some studies have shown that increased disease severity is associated with increased risk of reactivation.

PATHOPHYSIOLOGY

Cytomegalovirus belongs to *Betaherpesvirinae* subfamily. It is a double-stranded DNA virus and undergoes replication inside the host cell nucleus to produce characteristic large intranuclear inclusion body that is surrounded

by mansdocs.com

by a halo, giving rise to an "owl's eye" appearance. Cytoplasm may contain smaller granular inclusions. These cytomegalic cells are widely found in host organs like salivary glands, lungs, intestines, kidneys and liver. If the host immunity is compromised by disease or iatrogenic reasons, a variety of syndromes may be produced like pneumonitis, colitis, hepatitis, retinitis, encephalitis, etc. Patient develops a classical mononucleosis syndrome with appearance of atypical lymphocytes in the peripheral blood. It can also present as Guillain-Barré syndrome, myocarditis, thrombocytopenia and hemolytic anemia. CMV pneumonitis can complicate patients with acute respiratory distress syndrome.

Time of onset of CMV infection has generally found to be 4–28 days after ICU admission. Studies have shown that repeated (at least weekly) testing is required to monitor the reactivation phenomenon which may occur any time during the prolonged ICU course of critically ill patients.

The clinical significance of the viral infections, especially CMV infection, is unknown and remains debated, although CMV patients have significantly higher morbidity and mortality rates than the control group.

DIAGNOSIS

Cytomegalovirus infection is defined by any of the three methods: (i) positive viral cultures, (ii) antigenemia (detection of protein pp65), (iii) DNAemia by PCR from blood or another clinical specimen. Among viral cultures, antigenemia and PCR assay, later was found to detect CMV infection faster than rest of the two. Viral cultures are time consuming and have low sensitivity. Antigenemia assay is labor intensive; therefore, currently PCR assay is the most widely utilized method to monitor CMV infection.

Reactivation in blood has been more widely studied while data regarding CMV reactivation at other sites, particularly lungs are limited. However, it is suggested that reactivation in lungs might be more common and earlier than blood.

MANAGEMENT

Ganciclovir is the mainstay of treatment for CMV disease. It is a nucleoside analogue and acts by inhibition of DNA synthesis. Mode of treatment is intravenous therapy in patients with active disease. Adverse effects associated with the drug are fever, rash, diarrhea and hematological disturbances (neutropenia, anemia and thrombocytopenia). Neutropenia caused by ganciclovir is managed with granulocyte colony stimulating factor (G-CSF) and dose reduction. Second-line drugs include foscarnet, cidofovir or maribavir. Role of prophylactic (antiviral therapy in patients at risk) and preemptive treatment (antiviral therapy in patients with laboratory evidence of CMV infection) is not clearly defined for critically ill patients.

BIBLIOGRAPHY

1. Bone R. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med. 1996;24(7):1125-8.
2. Domart Y, Trouillet JL, Fagon JY, et al. Incidence and morbidity of cytomegaloviral infection in patients with mediastinitis following cardiac surgery. Chest. 1990;97(1):18-22.
3. Döcke WD, Pösch S, Fietze E, et al. Cytomegalovirus reactivation and tumor necrosis factor. Lancet. 1994;343(8892):268-9.
4. Ho M. Cytomegalovirus infection in patients with bacterial sepsis. Clin Infect Dis. 1998;26(5):1083-4.
5. Kutza A, Muhl E, Hackstein H, et al. High incidence of active cytomegalovirus infection among septic patients. Clin Infect Dis. 1998;26(5):1076-82.
6. Papazian L, Fraisse A, Garbe L, et al. Cytomegalovirus: an unexpected cause of ventilator-associated pneumonia. Anesthesiology. 1996;84(2):280-7.
7. Smith PD, Saini SS, Raffeld M, et al. Cytomegalovirus induction of tumor necrosis factor-alpha by human monocytes and mucosal macrophages. J Clin Invest. 1992;90:1642-8.
8. Stéphan F, Méharzi D, Ricci S, et al. Evaluation by polymerase chain reaction of cytomegalovirus reactivation in intensive care patients under mechanical ventilation. Intensive Care Med. 1996;22(11):1244-49.
9. Tanaka S, Toh Y, Minagawa H, et al. Reactivation of cytomegalovirus in patients with cirrhosis: analysis of 122 cases. Hepatology. 1992;16(6):1409-14.

by mansdocs.com

CHAPTER

55

Tropical Infections in ICU

Prashant Nasa, Dhruva Chaudhry

INTRODUCTION

In Indian subcontinent, the climate conditions or the exposure to contaminated water favors certain tropical infections. In last few decades, there is emergence of new and preexisting tropical diseases in sporadic and epidemic proportions; many of the intensive care units (ICUs) are receiving such patients with their severe form, particularly during epidemics. These patients are mostly young and otherwise healthy in their prime years of activity, hence unfavorable outcome is mostly unacceptable. The ICU management of these infections is thus extremely important and involves general organ support management and specific therapeutic intervention whenever available. In this chapter, the syndromic approach to tropical infections will be discussed first followed by few more common infections like leptospirosis, dengue fever, malaria, scrub typhus, tetanus, varicella and rabies will be discussed.

The severe presentation of tropical infections can present as multiorgan failure state and for the purpose of diagnosis can be classified into different syndromes.

FEVER WITH THROMBOCYTOPENIA

The infections in this group include dengue fever, leptospirosis, malaria, rickettsial infections and common viral fever. Theses diseases also present as hemorrhagic fever. The pathophysiology of thrombocytopenia includes immune destruction, bone marrow suppression, disseminated intravascular coagulation (DIC) drugs and sometimes hypersplenism. A useful distinguishing feature between malaria and leptospirosis is the presence of significant conjunctival hemorrhages in the latter. The platelet counts as low as 5,000/mm^3 can predispose the patient to life-threatening bleeding in the central nervous system or from the gastrointestinal and genitourinary tracts. There is lack of clear-cut guidelines on the transfusion thresholds of platelets, however the platelets transfusion can be considered with platelet count less than 20,000/mm^3 and 21,000–40,000/mm^3 with hemorrhagic manifestations. In malaria and leptospirosis, there could be associated derangement of coagulation pathway which can be monitored using prothrombin time (PT) and activated partial thromboplastin time (APTT) which needs to be corrected in bleeding patient.

FEVER WITH PULMONARY DYSFUNCTION

The infections that present with pulmonary dysfunction are severe falciparum malaria, leptospirosis, hantavirus infection, scrub typhus and severe pneumonias due to *Legionella* and the Pneumococcus. Acute respiratory distress syndrome (ARDS) is common and severe form of pulmonary involvement seen in tropical diseases. Incidence of ARDS in severe malaria is less than 2% to about 25% depending on the heterogeneity of the definition used for ARDS. ARDS in severe malaria may be a part of multiorgan dysfunction or more commonly often occurs within a few days of starting treatment and has been shown to have higher mortality rate. The incidence of ARDS with severe dengue fever is around 18–53% with antigen-antibody

by mansdocs.com

complex of dengue virus binding to alveolar lining cells that are responsible for increased permeability of the alveolar–capillary membrane seen in ARDS. In leptospirosis, pulmonary involvement includes ARDS and/or alveolar hemorrhage which is due to a combination of diffuse vasculitis, alveolocapillary injury and thrombocytopenia with mortality rate of 40–50%.

FEVER WITH HEPATORENAL DYSFUNCTION

The leptospirosis and malaria are the most common differential diagnosis and other diseases predominantly present with hepatorenal dysfunction include scrub typhus and fulminant hepatitis. The leptospirosis with elevated bilirubin and creatinine values and presence of altered consciousness, hemorrhages in the skin and mucous membranes (including conjunctiva) are strong possibilities for the physician to think. Renal failure in patients with severe malaria usually have oliguria in contrast to patients with leptospirosis, usually have a nonoliguric renal failure and caused by interstitial nephritis and tubular dysfunction. Liver involvement is characterized by centrilobular necrosis with proliferation of Küpffer cells. The hyperbilirubinemia seen in leptospirosis as compared to malaria tends to be more severe, as concomitant intravascular and extravascular hemolysis, hemorrhages and myoglobin released from the inflamed muscles.

FEVER WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

The common tropical infections under this syndrome are severe malaria (cerebral malaria), Japanese encephalitis (JE), typhoid fever, viral meningitis. The pathophysiology ranges from sequestration of parasitized red blood cells (RBCs) in cerebral microcirculation to neurologic invasion by the virus in Japanese encephalitis and postinfective demyelination syndromes with weakness or sensory disturbances in other tropical infections.

FEVER WITH SHOCK

The shock with multiorgan dysfunction is the most severe presentation and can be seen with leptospirosis, dengue fever, chikungunya fever, malaria, diarrheal disease. The pathophysiology of shock is similar to that in other causes of septic shock and includes a myriad of mediators, cytokines which induce intense vasodilatation, increase microvascular permeability and capillary leakage. This leads to absolute or relative intravascular hypovolemia and/or myocardial depression leading to inadequate tissue perfusion and oxygenation. Crystalloids (normal saline or lactated Ringer's solution) are the choice of resuscitation fluids and sufficient alone in majority of the patients; however, in severe tropical infections with profound shock, colloid solutions (5% albumin and hetastarch) can be tried with crystalloids but are expensive and no outcome benefit has been shown. Other management of shock is similar to that septic shock. The newer adjuvant therapies like ulinastatin, anti–D immunoglobulin in severe dengue or malaria have been tried in small cohort studies or in case series, however need bigger trials before they can be recommended.

MANAGEMENT OF SPECIFIC INFECTIONS IN ICU

Severe Falciparum Malaria

Incidence

The annual clinical caseload of malaria is estimated around 300–500 million people/year with 1.5–2.7 million annual deaths. Almost all deaths are due to falciparum malaria. Rarely, *P. vivax or P. ovale* cause serious morbidity and death. Africa has around 90% of the case load of falciparum infection, followed by Asia with approximately 80% of cases occurring in India.

Pathogenesis

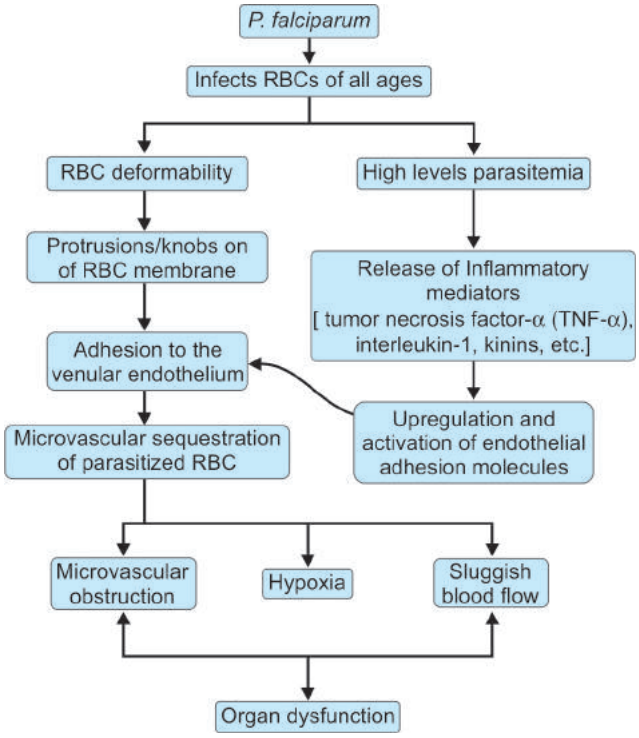
P. falciparum can infect RBCs of any age unlike other species, leading to high parasitic index and severe anemia (Flowchart 1) After 12–15 hours of RBC's invasion, *P. falciparum* malaria causes membrane protrusions on the RBC surface. The protrusions or knobs extrude a high–molecular–weight, antigenically variant, strain specific protein erythrocytic membrane adhesive protein (PfEMP1) which facilitates adherence to venular and capillary endothelium, a phenomenon termed as cytoadherence. The parasitized RBCs may also adhere to uninfected RBCs and to other parasitized RBCs to form rosettes (agglutination).

This results in microvasculature sequestration of RBCs containing mature form of the parasites in vital organs compromising the microcirculation. Also the parasites stimulate the production of cytokines including tumor necrosis factor (TNF) interleukin–1 and kinins.

by mansdocs.com

These cytokines suppress production of RBCs, increase fever and induce nitric oxide production, and upregulation and activation of endothelial adhesion molecules which in turn increase sequestration and adhesions to vascular endothelium. Eventually, this leads to microvascular sequestration, sluggish blood flow, obstruction and impaired O_2 delivery. The end result is organ dysfunction or organ failure with high morbidity or mortality.

Flowchart 1: Pathogenesis of severe malaria



Diagnosis

Thick and thin peripheral smears for degree of parasitemia and speciation. Tests for detecting *P. falciparum* antigens, e.g. *Plasmodium falciparum* histidine-rich protein-2 (*Pf*HRP-2) or *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) in blood from a finger prick. These tests use monoclonal antibodies to capture the parasite antigens and are highly sensitive and a negative test almost excludes malaria. Immunofluorescent microscopy and polymerase chain reaction (PCR) are newer techniques for detection of malaria.

Management

The WHO definition of severe falciparum malaria is based on clinic-laboratory criteria (Table 1). The need to recognize severe malaria is important as this allows the stratification and triaging of patients for optimal treatment to an ICU or high dependency unit (HDU). The ICU criteria of admission of severe malaria should be based on local infrastructure and clinical assessment (Table 2). The initial management of patient includes the initial stabilization of the patient using standard ICU protocols:

- Assess and maintain the airway, breathing and circulation
- Secure two wide bore cannula and take blood for emergency investigations that would help establish diagnosis, detect complications, and predict prognosis and

Table 1: WHO criteria for diagnosis of severe falciparum malaria

• Cerebral malaria	• Unarousable coma (GCS < 11/15) along with peripheral falciparum parasitemia after exclusion of other causes of encephalopathy
• Severe anemia	• Normocytic anemia with Hb < 5 g/dL, PCV < 15% in presence of parasitemia > 10,000/mL
• Respiratory distress	• Pulmonary edema or ARDS, now also include rapid labored "acidotic" breathing
• Renal failure	• Urine output < 400 mL in 24 hours and serum creatinine > 3 mg/dL
• Hypoglycemia	• Whole blood glucose < 40 mg/dL
• Circulatory collapse	• SABP < 70 mm Hg
• Coagulation failure	• Spontaneous bleeding and/or laboratory evidence of DIC
• *Complicated malaria*: Impaired consciousness of any degree, prostration, jaundice, intractable vomiting, parasitemia ≥ 2% in nonimmune individuals, i.e. no previous malaria	• Such patients should be managed as severe malaria with parenteral antimalarials even though they may not meet with the criteria of severe disease.

(GCS: Glasgow coma scale; PCV: Packed-cell volume; ARDS: Acute respiratory distress syndrome; SABP: Systemic arterial blood pressure; DIC: Disseminated intravascular coagulation).

by mansdocs.com

Table 2: Criteria for admission of patients with severe malaria to ICU

• Acidosis	• Base excess < -8
• Parasitemia	• Endemic areas: More than 20% Non-endemic areas: More than 10%
• Coma	• Glasgow coma score: ≤8
• Hypoglycemia	• Blood glucose level less than 2.2 mmoL/L
• Renal dysfunction	• Urine output less than 0.5 mL/kg/h
• Pulmonary edema	

emergencies. These include blood for the detection of malarial parasites, complete blood count, coagulation profile, arterial blood gases, serum lactates, electrolytes, renal and liver function tests.

- Do not delay the specific antimalarial therapy for parasitological confirmation and start immediately on the basis of clinical diagnosis.
- Assess and treat hypoglycemia.
- Assess the level of consciousness using a coma scale like Glasgow coma score (GCS) in adults and the Blantyre coma score (BCS) in children.
- Insert a urinary catheter to monitor the hourly urine output, feeding nasogastric tube, for medication, assessment of upper GI bleeding and for providing feeds. Insert a central venous pressure line for fluid administration, fluid assessment and arterial line if required.

Antimalarial therapy: Chloroquine resistance is now global phenomenon in falciparum malaria and hence all patients with severe malaria should be treated with artemisinin derivative with or without quinine. The revised guidelines released by WHO for treatment of malaria recommend the use of artemisinin compounds for severe falciparum malaria. The artemisinin derivatives include arteether, artemether and artesunate. The artemisinin derivatives offer a potent, rapid antimalarial activity, short half-life; hence good for combination with a wider therapeutic window along with an absence of clinically important drug resistance and considered a safer alternative to quinine.

Dose:

- *Artesunate*: 2.4 mg/kg IV/IM (0, 12 and 24 hrs) and then daily for 7 days
- *Artemether IM*: 3.2 mg/kg (0, 12 and 24 hours) followed by 1.6 mg/kg daily for 7 days
- *Quinine*: IV 20 mg/kg in 100 mL of 25% dextrose as a loading dose over 3–4 hours followed by 10 mg/kg in 25% dextrose over 3–4 hours 8 hourly. IM dose is similar to IV dose
- Monitor QTc interval.

In pregnancy as first line, artesunate and quinine are considered. In pregnant patients, the disease presentation is more severe with hypoglycemia and respiratory complications are common.

Management of Complications

Cerebral Malaria

Cerebral malaria may have variable presentations, altered sensorium, persistent coma, seizure. The cerebral malaria is considered if persistent changes in sensorium are not attributed to bacterial meningitis or viral encephalitis. Diffuse encephalopathy with frontal lobe signs may occur. The management includes supportive management as for any other comatose management. For the control of convulsions, phenytoin is used (15–20 mg/kg IV slowly, followed by 5 mg/kg IV 8 hourly or 12 hourly in divided dose as maintenance). The fever should can be controlled with tepid sponging and antipyretic agents and administer specific antimalarial therapy. There is no role of corticosteroids, anti-inflammatory drugs, drugs for cerebral edema (urea, mannitol), low-molecular-weight dextran, adrenaline and heparin for management of cerebral malaria.

Acute Kidney Injury

Acute Kidney injury (AKI) in malaria occurs as a component of severe disease with multiorgan failure and has a poor prognosis, or when parasitemia is declining. *P. falciparum* can cause mesangioproliferative glomerulonephritis (MPGN type I). The renal failure often nonoliguric. Early and frequent hemodialysis (HD) is required as renal failure is hypercatabolic and nonoliguric. The mortality of malarial AKI is 10–40%.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome is a fatal complication which occurs in severe falciparum malaria with a mortality rate as high as 80%. It may also occur in vivax malaria. The management involves early invasive ventilation and ventilation strategy as per ARDS net protocol. The iatrogenic hypoventilation is avoided in patients with raised intracranial pressure seen with cerebral malaria.

Anemia, Coagulopathy and DIC

Anemia in malaria is caused by hemolysis and inhibition of bone marrow production. Packed cell transfusion is indicated if packed cell volume (PCV) falls below 20% or

by mansdocs.com

Table 3: WHO definition of severe dengue fever

Probable dengue	*Warning signs*	*Severe dengue fever*
Live in/travel to dengue endemic area	• Abdominal pain or tenderness	*Severe plasma leakage leading to*:
Fever and two of the following:	• Persistent vomiting	• Shock (DSS)
• Nausea, vomiting	• Clinical fluid accumulation	• Fluid accumulation with respiratory distress
• Rash	• Mucosal bleed	• Severe bleeding as evaluated by clinician
• Aches and pains	• Lethargy, restlessness	
• Tourniquet test positive	• Liver enlargement >2 cm	
• Leukopenia	• Laboratory: increase in HCT	• Severe organ involvement

(DSS: Dengue shock syndrome; HCT: Hematocrit).

Hb below 7 g/dL. In severe malaria, blood coagulation pathways are almost always activated and almost universal thrombocytopenia, however, spontaneous bleeding or DIC is relatively uncommon. Coagulation defects and severity of thrombocytopenia often correlate with the degree of parasitemia. Prophylactic platelets transfusion in non-bleeding patients with malaria is not indicated unless platelet counts are below 10×10^9 μl^{-1}. If overt bleeding is present, fresh blood and frozen plasma transfusion, clotting factors and/or platelets are required. Vitamin K (10 mg) can be given intravenously for 3 days. Normally, thrombocytopenia occurs in malaria. Deranged liver function can also lead to deficit in the production of coagulation factors and albumin.

Hyperparasitemia

Hyperparasitemia is diagnosed if parasite index exceeds more than 5% in nonimmune subjects or more than 20% in normal individuals. Management of these patients involves parenteral antimalarial therapy irrespective of whether the patient can take the medication orally. Even after optimal antimalarial therapy, if condition deteriorates, plasma exchange can be considered.

Fluid and Electrolyte Disturbances

Hyponatremia is common in patients with severe malaria and the common causes are salt depletion, water dilution, syndrome of inappropriate antidiuretic hormone secretion and hypocalcemia is also a common feature of severe disease, often attributable to hypoalbuminemia. Attention should be paid to plasma potassium, calcium, magnesium and phosphate concentrations, especially when using quinine which causes hyperinsulinemia and glucose solutions which encourage potassium and phosphate to enter cells.

Shock or Circulatory Collapse

Some patients with severe malaria can present as shock and factors contributing to it are splenic rupture, bacterial septicemia, bleed, acute lung injury (ALI) or ARDS or severe metabolic acidosis due to AKI. In these patients:

- Correct hypovolemia with appropriate fluid therapy, if present.
- If patient does not respond to adequate fluid therapy, add vasoactive drugs.
- Look for possible sites of infection. Aspiration pneumonia should be considered in any unconscious patient with convulsions. Take appropriate cultures and start broad-spectrum antibiotics.
- If splenic rupture is confirmed, emergency splenectomy is done with volume and blood replacement.

Hypoglycemia

In severely ill patients, hypoglycemia commonly occurs together with metabolic (lactic) acidosis and decreases hepatic glycemic output, drugs like quinine carries a poor prognosis.

Equally susceptible are pregnant women and patients with severe disease. If require, administer 50 mL of 50% glucose solution followed by either 5% dextrose or 10% dextrose solution.

Severe Dengue Fever

World Health Organization (WHO) definition of severe dengue fever is given in Table 3.

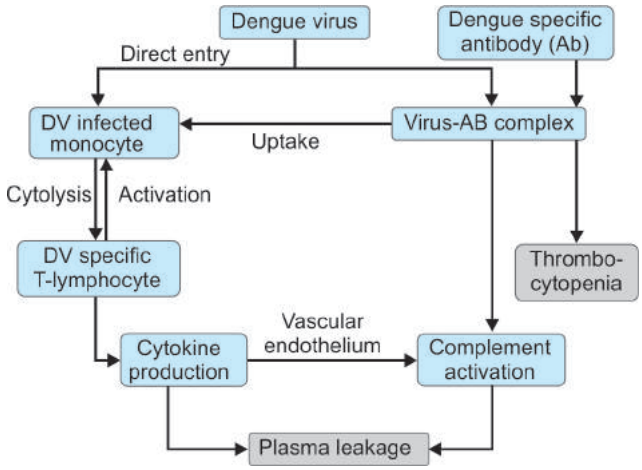
Pathogenesis: Pathogenesis is highlighted in Flowchart 2.

Diagnosis: The laboratory diagnosis can be carried out by one or more of the following tests:

- Isolation of dengue virus from serum, plasma, leukocytes or autopsy samples

by mansdocs.com

Flowchart 2: Pathogenesis



(DV: Dengue virus).

- Demonstration of a fourfold or greater rise in reciprocal IgG or IgM antibody titers to one or more dengue virus antigen in paired sera samples.
- Demonstration of dengue virus antigen in serum samples by enzyme-linked immunosorbent assays (ELISA) or in autopsy tissue by immunohistochemistry or immunofluorescence
- Detection of viral genomic sequences in autopsy tissue, serum or CSF sample by PCR.

Management: As dengue vascular permeability progresses, hypovolemia worsens and results in shock. It usually takes place around day 4 or 5 (range days 3–7) of illness, preceded by the warning signs. During the initial stage of shock, the compensatory mechanism maintains a normal systolic blood pressure by peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time. Uniquely, the diastolic pressure rises and the pulse pressure narrows as the peripheral vascular resistance increases.

In decompensated patients, both systolic and diastolic pressures fall significantly and if the hypotensive shock and hypoxia persists, it may lead to multiorgan failure. The presence of a pulse pressure ≤ 20 mm Hg indicates severe shock.

Hypotension is usually associated with prolonged shock, which is often complicated by major bleeding. Decompensated shock can be managed as per the Flowchart 3. The criteria for ICU admission are:

- Presentation with shock (on day 2 or 3 of illness)
- Severe plasma leakage and/or shock
- Undetectable pulse and blood pressure
- Severe bleeding
- Fluid overload
- Organ impairment (such as hepatic damage, cardiomyopathy, encephalopathy, encephalitis and other unusual complications).

Dengue Fever with Warning Signs

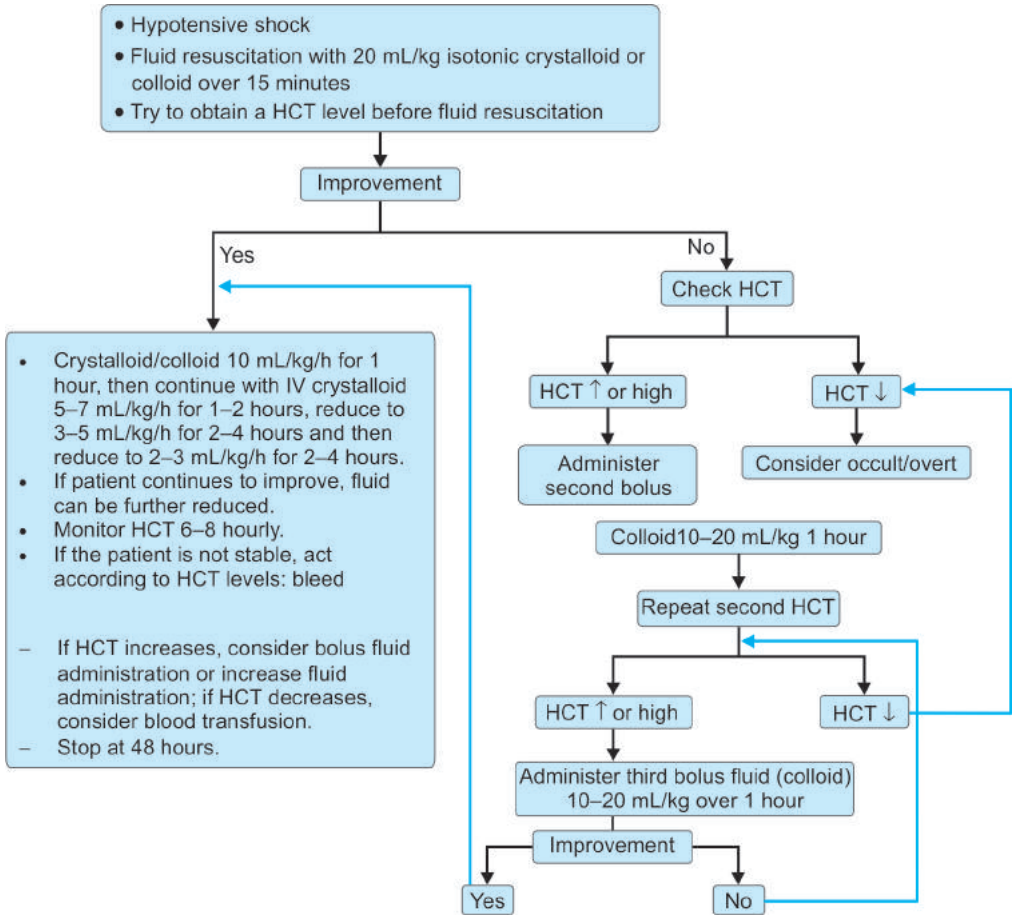
The patients with warning signs, those with coexisting conditions (such as pregnancy, infancy, old age, obesity, diabetes mellitus, renal failure, chronic hemolytic diseases), plan should be as follows: Obtain a reference hematocrit before fluid therapy. Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution. Start with 5–7 mL/kg/h for 1–2 hours, then reduce to 3–5 mL/kg/h for 2–4 hours and the reduce to 2–3 mL/kg/h or less according to the clinical response. Reassess the clinical status and hematocrit (Flowchart 4). If the hematocrit remains the same or rises only minimally, continue with the same rate (2–3 mL/kg/h) or another 2–4 hours. If the vital signs are worsening and hematocrit is rising rapidly, increase the rate to 5–10 mL/kg/h for 1–2 hours. Reassess the clinical status, hematocrit and fluid infusion rates accordingly. Give the minimum IV fluid volume required to maintain good perfusion and urine output of about 0.5 mL/kg/h. IV fluids are usually needed for only 24–48 hours. Reduce IV fluids gradually when the rate of plasma leakage decreases toward the end of the critical phase. This is indicated by urine output and/or oral fluid intake that is/are adequate or hematocrit decreasing below the baseline value in a stable patient.

Leptospirosis

This is a spirochetal disease caused by *Leptospira interrogans*. The spirochetes also infect rats, dogs, cattle, sheep and swine. Infection occurs due to exposure to contaminated water by urine of infected animal. The disease has an incubation period of 2–26 days (average of 10 days). Most patients have a nonspecific febrile illness, but in a few the disease manifests with a severe illness characterized by hepatorenal dysfunction often with pulmonary hemorrhage, called Weil's syndrome. The leptospires directly or through immune mechanisms damage blood vessels cause centrilobular necrosis of the liver and renal tubular dysfunction by causing an interstitial nephritis and acute tubular necrosis.

by mansdocs.com

Flowchart 3: Fluid resuscitation in decompensated shock (based on WHO guidelines)



(HCT: Hematocrit).

Clinical Features

Patients characteristically have conjunctival suffusion or hemorrhages and uveitis, severe muscle tenderness and nonoliguric renal failure with hypokalemia. Besides severe hepatorenal dysfunction, patients can present with ARDS, myocarditis, rhabdomyolysis, thrombocytopenia, DIC, hemorrhage into the skin and internal organs, uveitis and digital gangrene.

Laboratory Findings

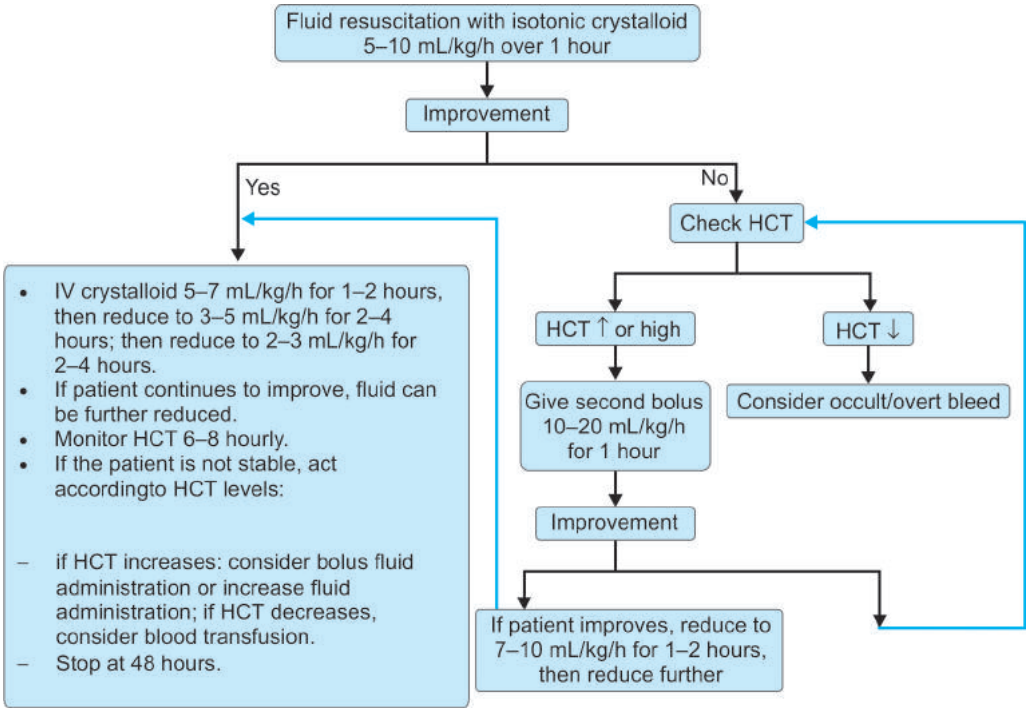
The white cell count is often less than 10,000. Urinalysis shows proteinuria, pyuria, granular casts and microscopic hematuria. The creatine phosphokinase (CPK) is often elevated, CSF may show aseptic meningitis like picture and the chest X-ray often shows dense confluent shadows suggestive of pulmonary hemorrhage.

Diagnosis

The diagnosis is made with serology with the microscopic agglutination test (MAT) as the gold standard with either a fourfold rise in titers or a single titer of more than 1:800 being diagnostic. Other serologic tests being the ELISA and a commercially available TRI-DOT test, which detects IgM antibody by an enzyme-based dot immunoassay with a sensitivity of 30% at 3 days and of 100% at 10 days into the illness. The organism can be grown from the blood and the CSF in the first 2 weeks of the illness and from the urine in the third week onward for up to a month. Since the antibodies may not be demonstrable in serum during the first week of illness, initial treatment is often empirical. In some patients, it is virtually impossible to differentiate between severe malaria and leptospirosis; this dilemma is compounded by the fact that the seasonal variation in the incidence of these two disorders is identical. These

by mansdocs.com

Flowchart 4: Fluid resuscitation in compensated shock (based on WHO guidelines)



(HCT: Hematocrit).

patients may receive treatment for both disorders on admission. We usually discontinue antimalarial treatment if several blood smears for malarial parasites over the next 48 hours are negative.

Treatment

It involves the use of crystalline penicillin at a dose of 6 million units daily or ceftriaxone 1 g every 12 hourly. In penicillin allergic patients, oral doxycycline 100 mg every 12 hour can be used. Since rickettsial diseases can mimic leptospirosis, ceftriaxone or doxycycline should be used when the diagnosis is in doubt. Other therapy involves supportive measures like dialysis, ventilation and the use of blood products.

Scrub Typhus

Also known as tsutsugamushi disease, this acute febrile disease is caused by *Orientia tsutsugamushi* which is a small Gram-negative, obligate intracellular organism, Gram-negative coccobacillus that infects vascular endothelium with subsequent vascular injury in organs like the skin, liver, kidneys, meninges and brain. The disease occurs 7–10 days after the bite and patients present with fever, relative bradycardia, severe myalgias, a nonpruritic maculopapular rash sometimes with an accompanying eschar and lymphadenopathy.

Complications

The patient may develop multisystem involvement, characterized by microangiopathies: focal vasculitis or perivasculitis.

Pulmonary involvement: Pleural effusion, bronchitis/interstitial pneumonitis, ARDS. ARDS is most severe involvement with mortality of 25–40% with risk factors for the development of ARDS are older age, thrombocytopenia and the presence of early pneumonitis.

Central nervous involvement: Encephalopathy, meningoencephalitis (mild pleocytosis, mild protein increase and normal sugar), cranial nerve deficits.

Renal involvement: AKI (interstitial nephritis).

Cardiac: Mainly subclinical but myocarditis and minor conduction disturbances can be seen.

Gastrointestinal: Hepatic dysfunction is common and rarely acute pancreatitis has been reported.

by mansdocs.com

Diagnosis

The diagnosis is made by history of exposure, appropriate physical findings, thrombocytopenia, deranged liver function tests, elevated creatinine and serology utilizing tests like immunofluorescence assay (IFA) and ELISA. The Weil-Felix reaction is now no longer used as a diagnostic tool.

Treatment

The treatment of choice is doxycycline (2.2 mg/kg/BD PO or IV, maximum 200 mg/day). The alternatives are chloramphenicol (50–100 mg/kg/day divided every 6 hours IV, maximum 3 g/24 hours), azithromycin (500 mg OD for 3 days) or rifampicin (600–900 mg OD).

CONCLUSION

The ICUs in developing countries like India have to be equipped with personnel, infrastructure and equipments to manage not only common infectious disease but also tropical diseases.

The understanding about the pathophysiology and management of complications is necessary for intensivist to decrease mortality associated with these diseases. The management relies on early suspicion and diagnosis by clinical and microbiologic methods. The institution of specific therapy must be complimented at times by supportive management.

BIBLIOGRAPHY

1. A review of WHO guidelines on management of malaria. Guidelines for diagnosis and treatment of malaria in India 2009.
2. Baghwati A. Falciparum Malaria in ICU. Medicine Update 2010: Vol 20. A Review on Management of Severe Falciparum Malaria in ICU.
3. Dengue guidelines by WHO. Dengue guidelines for diagnosis, treatment, prevention and control. 2009.
4. Kothari VM, Karnad DR, Bichile LS. Tropical infections in the ICU. J Asso Phy Ind. 2006;54:291-8.
5. Pasvol G. The treatment of complicated and severe malaria. Br Med Bull. 2006;75-76:29-47.
6. Rapsang AG, Bhattacharyya P. Scrub typhus. Indian J Anaesth. 2013;57:127-34.

by mansdocs.com

CHAPTER 56

Tropical Fever—Management Guidelines ISCCM Tropical Fever Group

Sunit Singhi, Dhruva Chaudhary, George M Verghese, Ashish Bhalla, SP Kalantri, JV Peter, Rajesh Chandra Mishra, Rajesh Bhagchandani, TD Chugh, Narendra Rungta, Manish Munjal

We have defined Tropical diseases as diseases that are prevalent in, or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation.[1] Most often disease is transmitted by an insect "bite", which causes transmission of the infectious agent through subcutaneous blood exchange. Indian subcontinent by its very location represents one of the largest tropical regions with many of these infections being prevalent. Some of them occur throughout the year and some are greatly influenced by the seasons (especially rainy season) and geography.[2] On basis of limited epidemiologic data from north (Rohtak) and South (Vellore) and overall experience of the group, it was decided to focus on six most common infections, with reference to other infections wherever appropriate.[3-5] These are dengue hemorrhagic fever, rickettsial infections/scrub typhus, Malaria (usually falciparum), typhoid, and leptospirosis; Bacterial sepsis and viral infections. It was recognized that sometimes the patients may have dual or triple infections and can present with atypical manifestations.[6-8]

Management of sick patients with tropical infections begins as soon as the patient reports to the emergency department/intensive care unit (ED/ICU) in a hospital. It is important to suspect these infections as delay in institution of specific therapy may lead to increased morbidity and mortality. Since the symptoms of many infections may overlap it may be very difficult clinically to identify these infections at the time of presentation. Most of the times, empiric therapy needs to be initiated at the outset. There can be no uniform guidelines for empiric therapy but trends of tropical infections should guide the treating physician. The idea is to **hit wide and hit early** with intention to de-escalate once the definitive diagnosis is established.[9]

We believe that a syndromic approach to tropical infections can guide the intensivists regarding the commonest etiologies, investigative modalities and help them to choose early empiric therapy. For ease of diagnosis, these infections can be divided into five major syndromes: Fever only, Fever with rash/thrombocytopenia, Fever with acute respiratory distress syndrome, Fever with encephalopathy and Fever with multiorgan dysfunction syndrome.[10] Infections that are likely to cause these syndromes are as follows:

Undifferentiated Fever

Malaria (*Plasmodium falciparum),* scrub typhus, leptospirosis, typhoid, dengue fever and other viral illness.

Fever with Rash/Thrombocytopenia

Bacterial infections, dengue hemorrhagic fever, rickettsial infections/scrub typhus, meningococcal infection, Malaria (usually falciparum), leptospirosis, typhoid, Crimean-Congo hemorrhagic fever and other viral fevers.

Fever with Acute Respiratory Distress Syndrome (ARDS)

Falciparum malaria, H1N1, leptospirosis, Hantavirus infection, scrub typhus, melioidosis. Tuberculosis, severe pneumonias due to *legionella* and *Pneumococcus*, Diffuse alveolar hemorrhage due to collagen vascular diseases.

by mansdocs.com

Febrile Encephalopathy

Bacterial infections, Herpes simplex virus encephalitis, Japanese B encephalitis, cerebral malaria, typhoid encephalopathy, fulminant hepatic failure due to viral hepatitis.

Fever with Multiorgan Dysfunction

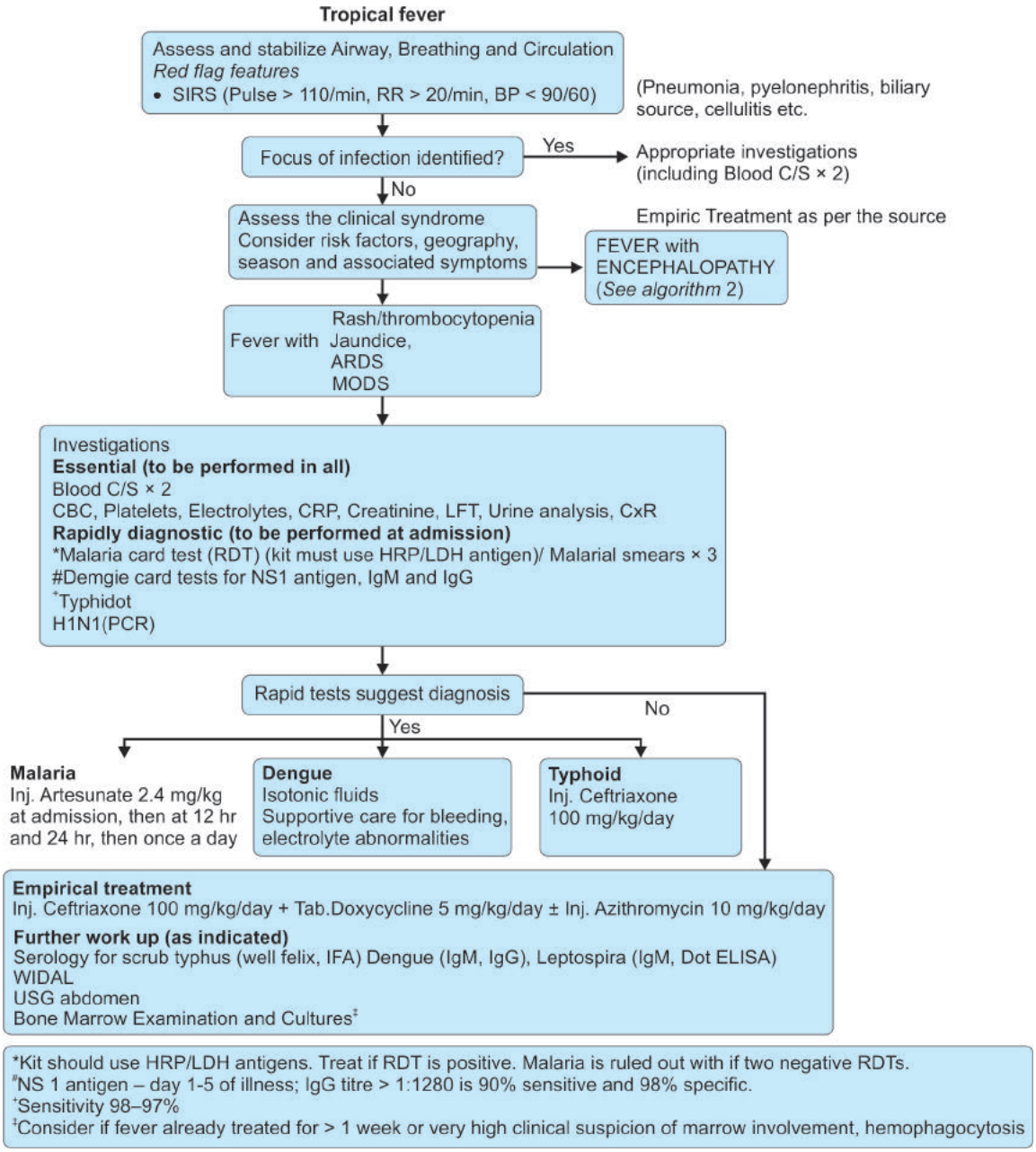
Bacterial sepsis, falciparum malaria, leptospirosis, scrub typhus, dengue, hepatitis A or E with fulminant hepatic failure and hepatorenal syndrome, Hantavirus, hemophagocytosis and macrophage activation syndrome.

An algorithmic approach for the diagnosis and management of critical tropical infections is given in Flowchart 1.

MANAGEMENT

Following are the syndrome-based management principles for critical tropical infections (Table 1).

Flowchart 1: An algorithmic approach for the diagnosis and management of critical tropical infections.



by mansdocs.com

Table 1: Syndromes-based management principles for critical tropical infections.

Fever with thrombocytopenia	• Antipyretics for control of fever • Intravenous (IV) fluids • Avoid aspirin/anticoagulants • Watch for bleeding, dyspnea, shock • Platelet transfusion if platelet count < 20,000 or clinical bleeding • No role of steroids • Specific therapy once diagnosis is established
Fever with jaundice	• Antipyretics for control of fever • Injection Ceftriaxone 2 g IV BD • Tablet doxycycline 100 mg BD • IV Fluids • Watch for urine output, seizures, encephalopathy, bleeding • Fresh frozen plasma (FFP)/Cryoprecipitate for bleeding • Specific therapy once diagnosis is established
Fever with renal failure	• Antipyretics for control of fever • Injection ceftriaxone 2 g IV BD • Tablet doxycycline 100 mg BD • IV Fluids according to Central venous pressure (CVP) • Watch for encephalopathy, bleeding, seizures, ARDS • Renal replacement therapy (Intermittent Hemodialysis/Continuous renal replacement therapy HD/CRRT) • Specific therapy once diagnosis is established
Fever with encephalopathy	• Antipyretics for control of fever • Injection ceftriaxone 2 g IV BD • IV Acyclovir 20 mg/kg intravenously every 8 hours • IV Fluids • IV Mannitol for raised intracranial pressure (ICP) • Watch for seizures • Specific therapy once diagnosis is established
Fever with respiratory distress	• Antipyretics for control of fever • IV Fluids • Oxygen by Venturi mask • Injection ceftriaxone 2 g IV BD • Injection azithromycin 500 mg IV OD • Tablet oseltamivir 150 mg BD, if H1N1 is a possibility • Watch for impending respiratory failure, shock, renal failure, alveolar hemorrhage • Specific therapy once diagnosis is established

SPECIFIC INFECTIONS

Salient features of common tropical infections are given below. An algorithmic approach to fever with encephalopathy is presented in the Flowchart 2.

SCRUB TYPHUS

Causative organism: Orientia tsutsugamushi

Vector: Chiggers (larva of Trombiculid mite).

Outbreaks are reported from all over India starting from the sub-Himalayan belt to more eastern and southern Indian regions.[11-13]

Pathophysiology: The organism infects vascular endothelium with subsequent vascular injury in organs like the skin, liver, kidneys, meninges and brain resulting in multiorgan manifestations.

Clinical features: Incubation period 1–3 weeks.

- Sudden onset of fever, headache and myalgia, Delirium, vomiting, cough and jaundice.
- Maculopapular rash—Begins on trunk and spreads to extremities (centrifugal spread).
- Eschar.

Complications: Overwhelming pneumonia with ARDS like presentation, myocarditis, and Disseminated intravascular coagulation (DIC).

Lab Diagnosis (Serology)[14]

- Weil-Felix: Poor sensitivity and specificity
- Indirect fluorescent antibody assay (IFA): "gold standard"
- Enzyme-linked immune sorbant assay (ELISA) for IgG and IgM antibodies: Sensitivity and specificity > 90%.

Treatment[15,16]

- First line: Doxycycline 100 mg BD for 7 days.
- Azithromycin or chloramphenicol as alternatives in children or pregnant women.

LEPTOSPIROSIS

Causative organism: Leptospira interrogan.

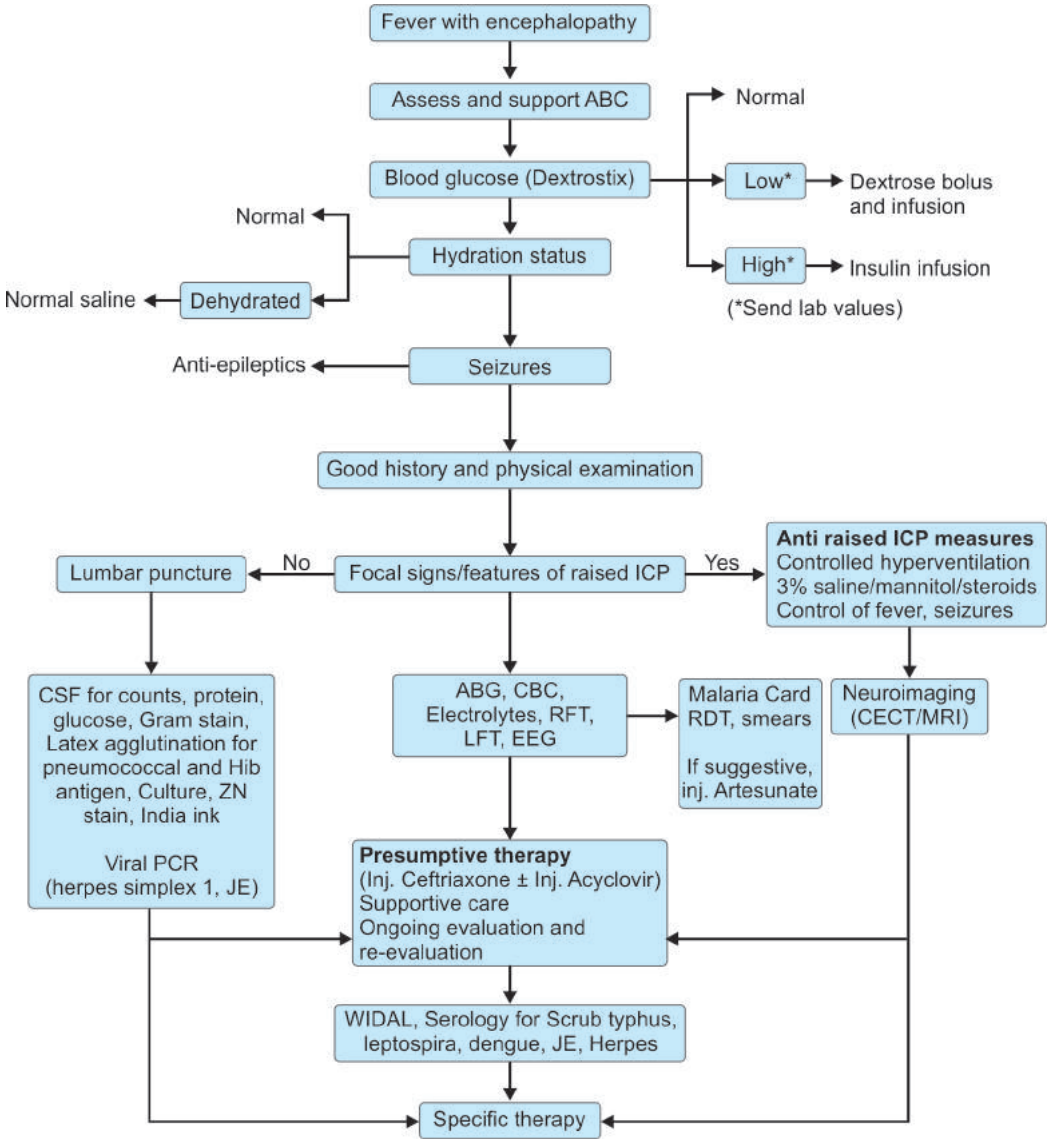
Source of infection: Urine or body fluid of an infected animal.

Peak incidence during rainy season. Rampant in southern, western and eastern India. Increasing incidence in "nonendemic" northern India.[17,18]

Pathophysiology: Leptospires multiply in the small blood vessel endothelium, resulting in damage and vasculitis and clinical manifestations.

by mansdocs.com

Flowchart 2: Algorithmic approach to fever with encephalopathy.



Clinical features: Incubation period: usually 5–14 days but can be 72 hours to a month or more.

Biphasic Clinical Presentation

Anicteric Leptospirosis

Abrupt onset of fever, chills, headache, myalgia, abdominal pain, conjunctival suffusion, transient skin rash.

Icteric Leptospirosis (Weil's disease)

Occurs in 5–15%—Jaundice, proteinuria, hematuria, oliguria and/or anuria, Pulmonary hemorrhages, ARDS, Myocarditis.

Diagnosis[19,20]

- Raised Creatine phosphokinase (CPK) levels, Culture [blood, cerebrospinal fluid (CSF), urine]
- Positive serology
  - Microscopic Agglutination Test (MAT)
  - IgM ELISA

Treatment[21,22]

First line therapy includes Penicillin G-1.5 MU 6 hourly for 7 days. The alternative, in case of penicillin allergy is third generation cephalosporins. Oral doxycycline can be used in uncomplicated infections. Other therapies like plasma

by mansdocs.com

exchange, corticosteroids, and intravenous immunoglobulins may be used in selected patients.

DENGUE

Causative organism: Dengue virus (Flavivirus) serotypes 1–4.

Vector: Aedes mosquitoes.

Dengue is endemic throughout India with a recent resurgence of epidemics over the past two decades.[23]

Pathogenesis:

- Cross-reactive (but non-neutralizing) anti-dengue antibodies from previous infection enhance newly infecting viral uptake of monocytes and macrophages.
- Amplified cascade of cytokines and complement activation.
- Endothelial dysfunction, platelet destruction, and consumption of coagulation factors, Plasma leakage and hemorrhagic manifestations.

Clinical features: Incubation period 4–10 days[24]

- Dengue fever
  - Headache, retro-orbital pain, myalgia, arthralgia, rash
- Dengue hemorrhagic fever
  - Thrombocytopenia (< 1,00,000), skin, mucosal and gastrointestinal (GI) bleeds, third spacing, rise in hematocrit.
- Dengue shock syndrome
  - Weak pulse, cold clammy extremities, pulse pressure < 20 mm Hg, hypotension
- Expanded dengue syndrome
  - Encephalitis, myocarditis, hepatitis, renal failure, ARDS, hemophagocytosis.

Diagnosis

- NS1 antigen detection (Rapid card test)[25]
- IgM, IgG serology

Treatment[26]

- Isotonic fluid infusion just sufficient to maintain effective circulation during the period of plasma leakage; guided by serial hematocrit determinations.
- Blood transfusion is done only with overt bleeding/rapid fall in hematocrit.

MALARIA

Causative organism: Plasmodium protozoa [P. falciparum, P. vivax, P. malariae (Odisha)].

Vector: Anopheles mosquito.

Plasmodium species are unevenly distributed across India. Orissa, Chhattisgarh, West Bengal, Jharkhand and Karnataka contribute the most to the endemicity.[27]

Pathophysiology:

- Mechanical microcirculatory obstruction caused by cytoadherence to the vascular endothelium of parasitized RBC and sequestration.
- Intravascular hemolysis.

Clinical features:

Paroxysm of fever, shaking chills, and sweats occur every 48 or 72 hours, depending on species. hepatosplenomegaly may be present.

Manifestations of severe malaria:[28]

1. Cerebral malaria (sometimes with coma)
2. Severe anemia
3. Hypoglycemia
4. Metabolic acidosis
5. Acute renal failure (serum creatinine > 3 mg/dL)
6. ARDS
7. Shock ("algid malaria")
8. DIC
9. Hemoglobinuria
10. Hyperparasitemia (> 5%)

Diagnosis:

- Microscopy: Thick smears—parasite detection; Thin smears—species identification.
- Quantitative buffy voat (QBC) test.
- Rapid diagnostic tests
  - Histidine rich protein (HRP), Lactate dehydrogenase (LDH) antigen based immune chromatography
  - Sensitivity and specificity > 95%
  - Malaria ruled out with two negative Rapid diagnostic tests
  - (RDTs).[29]

Treatment[28]

- Drug of choice: Artesunate
  - Dose: 2.4 mg/kg IV bolus at admission, 12 hours and 24 hours followed by once a day for 7days + Doxycycline 100 mg p.o. 12 hourly.
- Alternative: Quinine 20 mg/kg loading dose, followed by 10 mg/kg IV infusion 8 hourly + Doxycycline 100 mg 12 hourly.
- Clindamycin in place of Doxycycline in pregnant women and children.
- Exchange transfusion as a treatment option for parasitemia > 10%.

by mansdocs.com

ENTERIC FEVER

Causative organism: *Salmonella typhi, S. paratyphi A*.

Transmission: Focally contaminated food and water. Most prevalent in urban areas, with high incidence in children 15 years of age and younger.[30]

Pathophysiology: Bacteria spread throughout the reticuloendothelial system and in areas of greatest macrophage concentration such as the Peyer's patches.

Clinical features: Incubation period 1–14 days.

Manifestations

- First week—fever, headache, relative bradycardia.
- Second week—abdominal pain, diarrhea, constipation, hepatosplenomegaly, encephalopathy.
- Third week—intestinal bleeding, perforation, Multiorgan dysfunction syndrome (MODS).

Diagnosis[31]

- Typhidot (Rapid diagnostic test).
- Widal test: Nonspecific.
- Blood culture: Gold standard, positive in 40–80% of patients.
- Bone marrow cultures: Sensitivity 80–95%.

Treatment[32]

- Firstline: Ceftriaxone IV 50–75 mg/kg/day for 10–14 days.
- Aztreonam and Azithromycin are alternatives.
- Consider dexamethasone 3 mg/kg followed by 1 mg/kg 6 hourly for 48 hours in selected cases with encephalopathy, hypotension or DIC.

JAPANESE ENCEPHALITIS

Causative organism: Japanese encephalitis virus (JEV).

Vector: Culex tritaeniorhynchus. Prevalent in southern, central and north-eastern Indian states like Uttar Pradesh, Haryana, Bihar, Maharashtra, Andhra Pradesh and Tamil Nadu.[33]

Pathophysiology: Virus reaches the central neruous system (CNS) via leukocytes and affects various parts of the brain to cause vascular congestion, microglial proliferation, formation of gliomesenchymal nodules, focal or confluent areas of cystic necrosis and cerebral edema.

Clinical features: Incubation period averages 6–8 days, with a range of 4–15 days.

Prodromal period: Fever, headache, vomiting, and myalgia.

Neurological features[34]—range from mild confusion to agitation to overt coma. Parkinson like extrapyramidal signs are common, including mask like facies, tremor, rigidity, and choreoathetoid movements.

Diagnosis

IgM capture ELISA (serum and CSF).

Treatment

Supportive airway management, seizure control and management of raised intracranial pressure (ICP).

REFERENCES

1. Jaren Diamon. Guns, Germs and Steel: The Fates of Human Societies. New York: W.W Norton and Company; 1997.
2. Patz JA, Graczyk TK, Gellera N, et al. Effects of environmental change on emerging parasitic diseases. Int J Parasitol. 2000;30(12-13):1395-405.
3. Abrahamsen SK, Haugen CN, Rupali P, et al. Fever in the tropics: aetiology and case-fatality—a prospective observational study in a tertiary care hospital in South India. BMC Infect Dis. 2013;13:355.
4. Chrispal A, Boorugu H, Gopinath KG, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors—an experience from a tertiary care hospital in South India. Trop Doct. 2010;40(4):230-4.
5. John TJ, Dandona L, Sharma VP, et al. Continuing challenge of infectious diseases in India. Lancet. 2011;377(9761): 252-69.
6. Myers RM, Carey DE. Concurrent isolation from patient of two arboviruses, chikungunya and dengue type 2. Science. 1967;157(3794):1307-8.
7. Bhalla A, Sharma N, Sharma A, et al. Concurrent infection with dengue and malaria. Indian J Med Sci. 2006;60(8):330-1.
8. Kaur H, John M. Mixed infection due to leptospira and dengue. Indian J Gastroenterol. 2002;21(5):206.
9. Committee to Advice on Tropical Medicine and Travel. Canadian Recommendations for Fever in the returning International Travellers CCDR 2011;37:1-15.
10. Frean J, Blumberg L. Tropical fevers: Part A. Viral, bacterial and fungal infections. Primer of Tropical Medicine. ACTM publication; 2005. pp. 1-18. Available from http://www.tropmed.org/primer/chapter05a.pdf
11. Chaudhry D, Goyal S. Scrub typhus-resurgence of a forgotten killer. Indian J Anaesth. 2013;57(2):135-6.
12. Pandey D, Sharma B, Chauhan V, et al. ARDS complicating scrub typhus in Sub-Himalayan region. J Assoc Physicians India. 2006;54:812-3.

by mansdocs.com

13. Chrispal A, Boorugu H, Gopinath KG, et al. Scrub typhus: an unrecognized threat in South India—clinical profile and predictors of mortality. Trop Doct. 2010;40(3):129-33.
14. Koh GC, Maude RJ, Paris DH, et al. Diagnosis of scrub typhus. Am J Trap Med Hyg. 2010;82(3):368-70.
15. Rajapakse S, Rodrigo C, Fernando SD. Drug treatment of scrub typhus. Trop Doct. 2011;41(1):1-4.
16. Fang Y, Huang Z, Tu C, et al. Meta-analysis of drug treatment for scrub typhus in Asia. Intern Med. 2012;51(17): 2313-20.
17. Sethi S, Sharma N, Kakkar N, et al. Increasing trends of leptospirosis in northern India: a clinico-epidemiological study. PLoS Negl Trop Dis. 2010;4(1):e579.
18. Kalita JB, Rahman H. Leptospirosis among patients with pyrexia of unknown origin in a hospital in Guwahati, Assam. Indian J Public Health. 2008;52(2):107-9.
19. Chirathaworn C, Kaewopas Y, Poovorawan Y, et al. Comparison of a slide agglutination test, LeptoTek Dri-Dot, and IgM-ELISA with microscopic agglutination test for Leptospira antibody detection. Southeast Asian J Trop Med Public Health. 2007;38(6):1111-4.
20. Toyokawa T, Ohnishi M, Koizumi N. Diagnosis of acute leptospirosis. Expert Rev Anti Infect Ther. 2011;9(1):111-21.
21. Brett-Major DM, Coldren R. Antibiotics for leptospirosis. Cochrane Database Syst Rev. 2012;2:CD008264.
22. Charan J, Saxena D, Mulla S, et al. Antibiotics for the treatment of leptospirosis: systematic review and meta-analysis of controlled trials. Int J Prev Med. 2013;4(5):501-10.
23. Chakravarti A, Arora R, Luxemburger C. Fifty years of dengue in India. Trans R Soc Trop Med Hyg. 2012;106(5): 273-82.
24. World Health Organization and Special Programme for Research and Training in Tropical Diseases. Handbook for clinical management of dengue WHO and Special Programme for Research and Training in Tropical Diseases (TDR) report. November 2012. Available from http://apps.who.int/iris/bitstream/10665/76887/1/9789241504713_eng. pdf. Last accessed on 23 December 2013.
25. Singh MP, Majumdar M, Singh G, et al. NS1 antigen as an early diagnostic marker in dengue: report from India. Diagn Microbiol lnfect Dis. 2010;68(1):50-4.
26. Singhi S, Kissoon N, Bansal A. Dengue and dengue hemorrhagic fever: management issues in an intensive care unit. J Pediatr (Rio J). 2007;83(2 Suppl):S22-35.
27. Hay SI, Gething PW, Snow RW. India's invisible malaria burden. Lancet. 2010;376(9457):1716-7.
28. World Health Organization. Guidelines for the treatment of malaria. Second edition March 2010. Available from http://whqlibdoc.who.int/publications/201O/9789241547925_eng.pdf. Last accessed on 23 December 2013.
29. Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in endemic settings. Clin Microbiol Infect. 2013;19(5):399-407.
30. Kanungo S, Dutta S, Sur D. Epidemiology of typhoid and paratyphoid fever in India. J Infect Dev Ctries. 2008;2(6): 454-60.
31. Parry CM, Wijedoru L, Arjyal A, et al. The utility of diagnostic tests for enteric fever in endemic locations. Expert Rev Anti Infect Ther. 2011;9(6):711-25.
32. Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. J Postgrad Med. 2012;58(2):112-8.
33. Joshi R, Kalantri SP, Reingold A, et al. Changing landscape of acute encephalitis syndrome in India: a systematic review. Natl Med J India. 2012;25(4):212-20.
34. Sarkari NB, Thacker AK, Barthwal SP, et al. Japanese encephalitis (JE). Part I: clinical profile of 1,282 adult acute cases of four epidemics. J Neurol. 2012;259(1):47-57.

by mansdocs.com

SECTION 10

Ethics and End-of-Life Care Issues

by mansdocs.com

by mansdocs.com

CHAPTER

57

Bioethical Considerations

RK Mani, Prashant Saxena

INTRODUCTION

Ethical values and moral responsibilities of physicians toward their patients have been well-recognized since ages, and are mentioned in the Hippocratic Oath (400 BC), the Oath and Prayer of Maimonides (1783), Nuremberg code (1947), the Belmont Report for protection of human subjects of research (1979), and various national guidelines and codes for physicians.

Ethics deals with what is morally right and wrong conduct, what we ought to do and what we should refrain from doing. *Medical ethics* concerns with the moral issues involved in the care of patients.

Thus medical ethics includes:

- Principles of conduct and a guiding philosophy for physicians
- Rules of etiquette adopted by the medical profession to regulate professional conduct with each other, toward their individual patients and toward society
- Considerations of the motives behind that conduct.

Ethical principles underlying critical care practices have been well debated and firmly established. Among the four cardinal ethical principles followed in the West, particularly in the US, respect for patient's autonomy largely overrides the other three, namely beneficence, non-malfeasance and distributive justice.

Autonomy means the right to self-determination, where the informed patient has the *right to make choices* about the manner of his treatment. To be able to exercise his autonomy directly the patient should have the capacity to make decisions and choices. In many parts of the world, particularly in the US, in the event of the loss of his decision-making capacity, his autonomy is maintained by his wishes expressed in advance in the form of a will, or by his wishes as expressed by surrogates acting on his behalf ("substituted" judgment, i.e. "what would the patient want"). Substituted judgment does not imply personal preferences of the surrogates/proxy. Advance care planning, healthcare proxy, advance directives/living will in the US are tools to protect patient autonomy. In the *Quinlan* case, the US Supreme Court established the right of refusal of treatments whether unwanted or life-saving. Therefore, withdrawal of therapy is legally not killing but "allowing the patient to die" of the underlying illness. "Best interests" standards are expected to be applied where the patient's wishes and preferences cannot be ascertained. The right to self-determination is not so clearly stated in Indian law; however, the right to consent or to refuse treatment is established by common law, medical codes of conduct as well as by Law Commission Reports. Acting contrary to patient's wishes can be regarded as battery by Indian law.

Beneficence is conscientiously acting in a manner that would benefit patient. Critically ill patients carry a high risk of death. Therefore, beneficence should include consideration of the patient's pain, their physical and mental suffering, the risk of disability, and their quality of life as well as death. The physician, therefore, should not only address curative possibilities when they exist but also ensure appropriate care during the dying process. In this context, the physician's goals should be to facilitate (neither hasten nor delay) the dying process, and to avoid unwanted treatment and financial burdens for the patient and his family, and to provide timely emotional support.

by mansdocs.com

Universally, this practice is distinct from euthanasia which is defined as administration of the lethal injection by the physician as an act of mercy. Physician paternalism is the assumption of a protective role by the physician leading to unilateral action. Increasingly physician-patient relationship is moving away from a paternalistic one to that of an equal relationship leading to a shared responsibility. This has come about as the awareness of patient's rights as an individual and emphasis on autonomy has grown over the last two decades. In order to allow patient autonomy to prevail the physician is obliged to ensure that the patient is fully informed and empowered to participate in decision making.

Non-malfeasance: This is subject to varied interpretation, as the same act may be construed as harmful or beneficial depending on the circumstances. In the larger sense it does not limit itself to acts that may result in physiological harm but those that may cause injury to the patient as an individual. Therefore, in practical terms, it requires the physician not to act contrary to the patient's values and perspectives. While attempting to alleviate pain and distress the physician may often have to use drugs in large doses that may have unintended but foreseeable harmful effects. This cannot be interpreted as violation of the principle of non-malfeasance as the doctrine of double effect makes a distinction between intention and merely foreseen consequence. This is well-recognized by law in the US and Europe but in Indian law there is no reference to this principle. The right to be free from pain and suffering is widely recognized but the manner of its application is at present guided by professional ethics rather than by law.

Distributive justice means that all patients irrespective of their age, gender, race, ethnicity or station in life should receive similar treatment. In the presence of resource limitation a degree of rationing and prioritization can be allowed subject to auditing. This would also mean that cost considerations should be integrated into clinical practice so that there is as best an equitable distribution of resources as possible. As a corollary to this principle, the physician may prioritize allocation of resources to a potentially curable patient over another for whom it would be futile.

ROLE OF ETHICS COMMITTEE

Ethical issues and conflicts are not uncommon in the Indian scenario. Ethics committees may prove useful in resolving ethical conflicts. The committee consists of a multiprofessional team of responsible members who function as an independent "third party" which is not involved directly in the care of the patient. Such committees review the medical, ethical and psychosocial aspects of the case and provide an ethical analysis. They also provide, if required, counseling, social and emotional support to families explaining the ethical issues giving more time than the primary physicians. Sometimes, families may perceive a bias in favor of physicians or an attempt to protect the interests of the hospital. However, ethics committees are usually well received by both physicians and patients/surrogates. Ethics committees are associated with a decrease in the duration of intensive care unit (ICU) length of stay and use of life-prolonging treatments for terminally ill patients who do not survive.

COMMUNICATION

The importance of effective communication with families of critically ill patients is well-recognized and understood. However, communication is one of the most frequently ignored aspects of patient care in Indian ICUs.

Communication is central to treatment plans, prognostication and consent for interventions, discussing risks and benefits. In the critical care context, 95% of patients by virtue of being partially or totally incompetent are dependent upon their families for communication with caregiver team. In the context of end of life care, communication becomes even more crucial to a shared decision making. Through the medium of repeated family conferencing, the caregiver team is able to integrate the values and preferences of the patients communicated through surrogates. Interestingly, studies by Azoulay et al. showed that more than half the families and patient representatives do not fully understand the prognosis and treatment plan. Therefore, for the sake of clarity and for reducing anxiety and stress among family members, family conferences are an essential part of such decision making. Physicians are more likely to achieve effective communication when meetings begin earlier in the course of care. In one study, proactive, formal, multidisciplinary meetings held within 72 hours of ICU admission for patients with a predicted ICU stay longer than 5 days, or predicted mortality greater than 25%, decreased ICU length of stay and allowed earlier access to palliative care. Consistent proactive communication with families for updates on progress and encouragement to use advanced support when appropriate is recommended. Improved communication can also be facilitated by using a private place for discussion, listening, empathetic interaction, acknowledging family emotions, focusing on patient values and treatment preferences, clear explanation of

by mansdocs.com

the principle of surrogate decision making, assurance that the patient will not suffer, and support for the decisions made by the family. A simplified mnemonic for important elements of effective physician family communication in terms of content and quality is VALUE (Value and appreciate what is said by family members, Acknowledge the family members' emotions, Listen, Understand who the patient is as a person, Elicit questions from the family members). Families of ICU patients suffer and may develop long-term mental health issues related to the trauma of witnessing the ICU treatment or end-of-life care of a loved one. Symptoms can include posttraumatic stress disorder (PTSD), anxiety and depression. It is now clear that physicians must accept responsibilities through proactive communication and appropriate emotional support to family members involved in end-of-life decision making. In one multicenter trial, proactive end-of-life conferences with relatives of patients dying in French ICUs resulted in better long-term psychological outcomes in the family members when compared with customary practices.

BIBLIOGRAPHY

1. Azoulay E, Chevret S, Leleu G, et al. Half the families of intensive care unit patients experience inadequate communication with physicians. Crit Care Med. 2000;28(8):3044-9.
2. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of posttraumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005; 171(9):987-94.
3. Carlet J, Thijs LG, Antonelli M, et al. Challenges in end-of-life care in the ICU. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003. Intensive Care Med. 2004;30(5):770-84.
4. Crippen D, Kilcullen JK, Kelly DF (Eds). Three Patients: International Perspectives on Intensive Care at the End of Life. Boston, MA: Kluwer Academic Publishers; 2002.
5. Curtis JR, Engelberg RA, Wenrich MD, et al. Missed opportunities during family conferences about end-of-life care in the intensive care unit. Am J Respir Crit Care Med. 2005; 171(8):844-9.
6. Curtis JR, White DB. Practical guidance for evidence-based ICU family conferences. Chest. 2008;134(4):835-43.
7. Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004-2005. Crit Care Med. 2007;35(2): 605-22.
8. Ferrand E, Robert R, Ingrand P, et al. Withholding and withdrawal of life support in intensive-care units in France: a prospective survey. French LATAREA Group. Lancet. 2001; 357(9249):9-14.
9. Glavan BJ, Engelberg RA, Downey L, et al. Using the medical record to evaluate the quality of end-of-life care in the intensive care unit. Crit Care Med. 2008;36(4):1138-46.
10. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. N Engl J Med. 2007;356(5):469-78.
11. Lilly CM, De Meo DL, Sonna LA, et al. An intensive communication intervention for the critically ill. Am J Med. 2000;109(6):469-75.
12. Luce JM, Alpers A. Legal aspects of withholding and withdrawing life support from critically ill patients in the United States and providing palliative care to them. Am J Respir Crit Care Med. 2000;162(6):2029-32.
13. Luce JM, Lemaire F. Two transatlantic viewpoints on an ethical quandary. Am J Respir Crit Care Med. 2001;163(4): 818-21.
14. Mani RK, Amin P, Chawla R, et al. Guidelines for end-of-life and palliative care in Indian intensive care units' ISCCM consensus Ethical Position Statement. Indian J Crit Care Med. 2012;16(3):166-81.
15. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. Crit Care Med. 2004;32(7):1484-8.
16. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. Crit Care Med. 2001;29(10):1893-7.
17. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. Am J Respir Crit Care Med. 1997;155(1):15-20.
18. Schneiderman LJ, Gilmer T, Teetzel HD, et al. Effect of ethics consultations on nonbeneficial life-sustaining treatments in the intensive care setting: a randomized controlled trial. JAMA. 2003;290(9):1166-72.
19. Schneiderman LJ, Gilmer T, Teetzel HD. Impact of ethics consultations in the intensive care setting: a randomized, controlled trial. Crit Care Med. 2000;28(12):3920-4.
20. Stapleton RD, Engelberg RA, Wenrich MD, et al. Clinician statements and family satisfaction with family conferences in the intensive care unit. Crit Care Med. 2006;34(6): 1679-85.
21. Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College [corrected] of Critical Care Medicine. Crit Care Med. 2008;36(3):953-63.

by mansdocs.com

CHAPTER

58

End-of-Life Care Practices in the World

RK Mani, Prashant Saxena

INTRODUCTION

There is a shift of paradigm in critical care from a technology-centered curative care to a more comprehensive care of the patient that includes palliative and comfort care in terminally ill or dying patients.

The approach has shifted to identify the point at which aggressive therapies must cease and give way to greater and greater degree of palliative/comfort care. This has happened because more and more people are found to die using intensive care. The USA national survey has shown that one out of every five American, and 10% of those that are hospitalized die in intensive care. Simultaneously, we have witnessed the emergency of the hospice movement in the USA to the point that today 30% of the elderly die utilizing hospice care and this trend is increasing.

Managing death to ensure comfort and quality of the manner of death has led to the culture in the US and Europe, of limiting life support in 75–90% of the deaths. In the US, the first do not resuscitate order was written in 1976. This was followed by a codified law allowing do not attempt resuscitation (DNAR) in 1988, and subsequently by the increasing focus on patient preferences and autonomy.

Forgoing of life support decisions increased two-fold in the 90s as compared to late 80s. Presently, the quality of dying and death (QODD) is increasingly being accepted as one of the quality indices in critical care. The CoBaTrICE initiative had identified several skill sets in palliative care, end-of-life discussions (EOLD) making and communication as essential to the training of intensivists. The ETHICUS study revealed that up to 75% of deaths in European intensive care units (ICUs) take place preceded by an EOLD. But wide variations in practice revealed that greater proportion of EOLD remains in north European as compared to southern countries. Similar variations were also seen in surveys in the US. Reports from various parts of the world in China, Hong Kong, Israel, Saudi Arabia and India have revealed cultural variations in the EOLD rates but it is evident that the practice of forgoing of life-sustaining therapies (FLST) is now a universal phenomenon. Several professional societies have published guidelines/position statements on FLST and palliative care of terminally ill patients in critical care units. Several countries have legislations and legal framework laid down for the protection of patient and physician interests. Research on end-of-life care (EOLC) and FLST has come into the mainstream and has attracted funding. Publications in this area of critical care have witnessed an exponential rise. Much debate has been centered around the balance between patient autonomy and physician control over these decisions. It is now abundantly clear that autonomy predominates in the practices in the US while it is less pronounced in some countries such as France, UK and South Africa. There is general consensus, however, that a balanced approach is required wherein a physician-family shared decision making depending upon the cultural sensitivities of the region. Studies have revealed that a greater degree of paternalism is expected in some cultures such as the Chinese. It is also clear that cultural environment may impact upon the predominance of a certain type of FLST, e.g. withdrawal of continuous life support being less acceptable in Israel as compared to the UK. Research also further focused on the timing of these decisions.

by mansdocs.com

Family satisfaction parameters point to the need of early discussion and decision making during the course of patient stay rather than a delayed one. Crucial to all these decisions is adequate communication in terms of duration, frequency and content. Because most patients in the ICU are found to have lost their capacity and are therefore dependent upon their preferences being voiced by their family. Family conferencing with physicians becomes central to such decision making. The US law is fairly clear about the role of the surrogates. They are expected to truly represent the patient's preferences and choices rather than expressed their own. The physician must balance the patient choices and the best interest of the patient in arriving at a consensus decision.

Since these decisions are complex, EOLC demands the same level of knowledge, expertise and training as any other area of critical care. Pathways to EOLD making have been published to aid the caregiver team. Two concerns about patient care following an EOLD decision have been addressed. The first one is that those with an EOLD may get suboptimal care. This was dispelled by one paper that there is no reduction in the quality indices after such decisions. A multicentered Italian study showed that ICUs with predilection for EOLD had lower standardized mortality ratio as compared to those who did not. This would suggest that the overall quality of care in the unit only tends to improve with careful considerations of risks versus benefit in therapeutic interventions avoiding unwanted and burdensome therapies.

Another important principle of EOLD in practice is ensuring control of pain, distress and dyspnea. EOLD would lose its purpose if not followed by a liberal use of analgo-sedation. Because of the ambiguity of beneficence versus non-maleficence in the use of drugs that may cause unintended physiological harm, ethical and legal issues have been raised. In the US law as with several other countries the principle of double effect is invoked for clarity on this issue. The physician is not culpable if in his efforts to provide optimal palliative care, unintended harm accrues to the patient. It would be difficult to prove intention except through providing meticulous documentation of the drugs, doses and targets. In general, although the use of drugs should be liberal, it should not exceed the recommended dose range.

Presently, active shortening of the dying process, physician-assisted suicide and euthanasia are modalities that are practiced and legally allowed in only a few regions of the world. Questionnaires revealed that health care practitioners have often expressed the intention to actively shorten dying process. However, this enters into an area of uncertainty in EOLD. Physician-assisted suicide and euthanasia have legal sanctions in the Netherlands and in the state of Oregon in the US, but it requires consent from a patient in his full capacity and cannot, therefore, be applicable in critical care.

Advance will is an instrument through which a patient can document his wishes while he is in his full capacity in anticipation of a situation where aggressive life support may be required. Although advance will or durable power of attorney is useful instrument to safeguard patient autonomy, in practice there are several pitfalls. The patient may not document his wishes in a fully informed state or may not be able to visualize the critical care situations. In any case, implementation of his wishes is heavily dependent upon the caregiving team and his surrogates.

Researches showed that advance care planning has considerably facilitated EOLC. This involves providing a patient with chronic debilitating illness with an opportunity to discuss the prognosis and the trajectory of his illness as well as his choices in the event of needing life support interventions. Such planning in the context of advance cancer has shown lesser utilization of ICU and fewer rate of cardiopulmonary resuscitation (CPR) in patients with advance care planning.

by mansdocs.com

SECTION 11

Miscellaneous

by mansdocs.com

by mansdocs.com

CHAPTER 59

Burns, Inhalation and Electrical Injury

Diptimala Agarwal

INTRODUCTION

Burns are one of the most devastating conditions in terms of morbidity and mortality and can lead to lifelong disfigurement and functional loss in survivors. It affects all ages from infants to elderly people, and is a problem in both the developed and developing world. Burn injuries require a skilled multidisciplinary team approach.

PREVALENCE

In the developed world 25,000 people in United Kingdom get burnt every year, and the USA 300 people die due to burn in a year.

In the developing world 2 million burn injuries are reported in a year in India, and in Nepal 1,700 burn deaths occur in a year.

CAUSES

- Flames—55%
- Scalds—40%
- Chemicals—5%
- Electrical—5%

INCIDENCE OF BURNS

Incidence of burn by age are:

- 1–4 years old—20%
- 5–14 years old—10%
- 15–64 years old—60%
- More than 65 years old—10%

Young Children

Children aged up to 4 years comprise 20% of all patients with burn injuries. Most injuries are scalds due to children spilling hot liquids or being exposed to hot bathing water. Boys are more likely to be injured, a reflection of the behavioral differences between boys and girls.

Older Children and Adolescents

Some 10% of burns happen to children between the ages of 5 years and 14 years. Teenagers are often injured from illicit activities involving petrol or electrocution.

Working Age

Most burns (>60%) occur in patients aged 15–64 years. These are mainly due to flame burns, and up to one-third are due to work-related incidents.

Elderly People

Some 10% of burns occur in people aged over 65 years. Various effects of ageing (such as immobility, slowed reactions and decreased dexterity) mean elderly people are at risk from scalds, contact burns and flame burns.

Compromising Factors

Some factors such as alcoholism, epilepsy, or chronic psychiatric or medical illness can affect the health of a burn victim.

by mansdocs.com

AIMS OF BURN CARE

- Restore form—Return the damaged area to as close to normal as is possible
- Restore function—Maximize patient's ability to perform preinjury activities
- Restore feeling—Enable psychological and emotional recovery.

The burn management can be divided into seven phases (seven Rs):

1. *Rescue*: The aim is to get the individual away from the source of the injury and provide first aid. This is often done by nonprofessionals—friends, relatives, bystanders, etc.
2. *Resuscitate*: Immediate support must be provided for any failing organ system. This usually involves administering fluid to maintain the circulatory system but may also involve supporting the cardiac, renal and respiratory systems.
3. *Retrieve*: After initial evacuation to an accident and emergency department, patients with serious burns may need transfer to a specialist burns unit for further care.
4. *Resurface*: The skin and tissues that have been damaged by the burn must be repaired. This can be achieved by various means from simple dressings to aggressive surgical debridement and skin grafting.
5. *Rehabilitate*: This begins on the day a patient enters hospital and continues for years after he or she has left. The aim is to return patients, as far as is possible, to their preinjury level of physical, emotional and psychological well-being.
6. *Reconstruct*: The scarring that results from burns often leads to functional impairment that must be addressed. The operations needed to do this are often complex and may need repeating as a patient grows or the scars reform.
7. *Review*: Burn patients, especially children, require regular review for many years so that problems can be identified early and solutions provided.

PATHOPHYSIOLOGY

Local Response

The three zones of a burn were described by Jackson in 1947.

1. *Zone of coagulation*: This occurs at the point of maximum damage. In this zone, there is irreversible tissue loss due to coagulation of the constituent proteins.
2. *Zone of stasis*: The surrounding zone of stasis is characterized by decreased tissue perfusion. The tissue in this zone is potentially salvageable. The main aim of burns resuscitation is to increase tissue perfusion here and prevent any damage becoming irreversible. Additional insults—such as prolonged hypotension, infection, or edema—can convert this zone into an area of complete tissue loss.
3. *Zone of hyperemia*: In this outermost zone tissue perfusion is increased. The tissue here will invariably recover unless there is severe sepsis or prolonged hypoperfusion. These three zones of a burn are three dimensional, and loss of tissue in the zone of stasis will lead to the wound deepening as well as widening.

Systemic Response

The release of cytokines and other inflammatory mediators at the site of injury has a systemic effect once the burn reaches 30% of total body surface area (TBSA).

Cardiovascular Changes

Capillary permeability is increased, leading to loss of intravascular proteins and fluids into the interstitial compartment. Peripheral and splanchnic vasoconstriction occurs. Myocardial contractility is decreased, possibly due to release of tumor necrosis factor. These changes, coupled with fluid loss from the burn wound, result in systemic hypotension and end-organ hypoperfusion.

Respiratory Changes

Inflammatory mediators cause bronchoconstriction, and in severe burns adult respiratory distress syndrome can occur.

Metabolic Changes

The basal metabolic rate increases up to three times its original rate. This, coupled with splanchnic hypoperfusion, necessitates early and aggressive enteral feeding to decrease catabolism and maintain gut integrity.

Immunological Changes

Nonspecific downregulation of the immune response occurs, affecting both cell-mediated and humoral pathways.

by mansdocs.com

MECHANISMS OF INJURY/TYPES OF BURNS

Thermal Injuries

Scalds Injury

- Most common cause of thermal injury
- Mostly partial thickness, but deeper injury more common in children and elderly
- Full thickness burn is often patchy and early diagnosis difficult.

Flame Burn

- Most common cause of fatal injury
- Generally full thickness
- Associated inhalation injury occurs in enclosed space
- Potential for circumferential limb/chest/neck injury.

Flash Burn

- Explosion injury without clothing fire
- Full or partial thickness
- Commonly face and hands
- Suspect injury as in blunt trauma because of explosive force.

Contact Burn

- Victim commonly unconscious (alcohol, epilepsy, drugs)
- Often full thickness
- Suspect compartment syndrome because of prolonged pressure.

Electrical Injury

- High (>1,000 V) or low (<1,000 V) tension
- High tension causes dramatic tissue destruction
- Entry/exit wounds are sites of focal skin burn
- Muscle damage often severe and occult
- Muscle necrosis causes myoglobinuria or acidosis with renal failure
- Suspect compartment syndrome
- Arrhythmias in one-third of patients with high-tension injury. Myocardial damage is rare. Arrhythmia is rarely dangerous if patient reaches hospital
- Domestic (low tension) electricity commonly causes small burns to the periphery without muscle damage.

Chemical Injury

- Becomes deep without appropriate first aid. High volume water irrigation for at least 30 minutes (optimum temperature is 15°C, prevent hypothermia in children)
- Hydrofluoric acid burn is very uncommon but very important. May cause fatal hypocalcemia even in a relatively small cutaneous burn. Immediate excision and monitoring may be necessary. Inhalation, chemical or electrical burns are classified by body surface area (BSA) and depth.

Body Surface Area

The "rule of nines" enables rapid initial estimation of the burn area in adults. Lund and Browder charts are used to estimate burn area in children and to provide a more precise estimate in adults. Lund and Browder charts are age-specific and take into account children's disproportionate BSA, larger heads and smaller arms, legs and torso. In the early postburn period, it is often difficult to estimate the full extent and depth of burns.

Depth

A superficial burn affects only the epidermal layer and is red, painful, dry and with no blisters. Healing occurs within a week.

A *partial thickness burn* involves the epidermal and dermal layers and can be classified as shallow or deep depending on the extent of damage to the dermis. The skin is red, blistered and painful and edema is present. Healing occurs in 14 days with no scarring after a shallow burn and in 4 weeks with scarring after a deep burn, which may also require excision and grafting.

A full thickness burn destroys all layers of the skin whereas a complex full thickness burn involves subcutaneous tissues and muscles. The burn appears white and pricking the skin with a needle causes no bleeding. Skin grafting is required to treat this burn.

DEFINITION OF A MAJOR BURN

- Requiring referral to a specialist burns center
- Full thickness burn more than 10% TBSA
- Partial thickness burn involving more than 25% TBSA in adults and more than 20% TBSA at the extremes of age

by mansdocs.com

- Burns to the face, hands, perineum or feet
- Burns affecting a major joint.

INITIAL MANAGEMENT OF A MAJOR BURN

History Taking

The history of a burn injury can give valuable information about the nature and extent of the burn, the likelihood of inhalational injury, the depth of burn, and probability of other injuries. The exact mechanism of injury and any prehospital treatment must be established. A patient's history must be obtained on admission, as this may be the only time that a firsthand history is obtainable.

Swelling may develop around the airway in the hours after injury and require intubation, making it impossible for the patient to give a verbal history. A brief medical history should be taken, outlining previous medical problems, medications, allergies and vaccinations. Patient's smoking habits should be determined as these may affect blood gas analyses.

Primary Survey

Establish A, B, C, D, E and F. The burn wound does not take priority above potential life-threatening injuries.

A—Airway with Cervical Spine Control

An assessment must be made as to whether the airway is compromised or is at risk of compromise. The cervical spine should be protected unless it is definitely not injured. Inhalation of hot gases will result in a burn above the vocal cords. This burn will become edematous over the following hours, especially after fluid resuscitation has begun. This means that an airway that is patent on arrival at hospital may occlude after admission. This can be a particular problem in small children.

Direct inspection of the oropharynx should be done by a senior anesthesiologist. If there is any concern about the patency of the airway then intubation is the safest policy. However, an unnecessary intubation and sedation could worsen a patient's condition, so the decision to intubate should be made carefully.

B—Breathing

All burn patients should receive 100% oxygen through a humidified non-rebreathing mask on presentation. Breathing problems are considered to be those that affect the respiratory system below the vocal cords. There are several ways that a burn injury can compromise respiration.

Mechanical restriction of breathing: Deep dermal or full thickness circumferential burns of the chest can limit chest excursion and prevent adequate ventilation. This may require escharotomies.

Blast injury: If there has been an explosion, blast lung can complicate ventilation. Penetrating injuries can cause tension pneumothoraces, and the blast itself can cause lung contusions and alveolar trauma and lead to adult respiratory distress syndrome.

Smoke inhalation: The products of combustion, though cooled by the time they reach the lungs, act as direct irritants to the lungs leading to bronchospasm, inflammation and bronchorrhea. The ciliary action of pneumocytes is impaired, exacerbating the situation. The inflammatory exudate created is not cleared, and atelectasis or pneumonia follows. The situation can be particularly severe in asthmatic patients. Noninvasive management can be attempted with nebulizers and positive pressure ventilation with some positive end-expiratory pressure.

However, patients may need a period of ventilation, as this allows adequate oxygenation and permits regular lung toileting.

Carboxyhemoglobin/Carbon monoxide poisoning: Carbon monoxide (CO) poisoning is responsible for 80% of deaths associated with smoke inhalation. CO has an affinity that is 250 times that of O_2 for hemoglobin (Hb); it also shifts the oxyhemoglobin (HbO_2) dissociation curve to the left. It, therefore, greatly reduces the amount of O_2 available for metabolism, causing tissue hypoxia and metabolic acidosis. Tissue hypoxia occurs from displacement of oxygen from hemoglobin, and the inhibition of complex IV in the respiratory chain in mitochondria. Clinical symptoms depend on the amount of CO present: 10–20% tinnitus, headaches and nausea; 20–40% weakness and drowsiness more than 40% coma, convulsions and cardiac arrest.

Only direct CO-oximeters using multiwavelength spectroscopy can differentiate Hb, HbO_2 and carboxyhemoglobin (HbCO). Pulse oximeters will indicate the oxygen saturation of HbO_2 but will give no indication of the true oxygen content of the blood because HbCO is not detected. Thus, the total hemoglobin oxygen saturation is overestimated.

Treatment is by high concentration O_2 therapy which will decrease the half-life of CO from 2 hours to 30 minutes. Three hyperbaric oxygen (HBO) treatments given over a

by mansdocs.com

24-hour period reduce neurological sequelae in patients with symptomatic acute CO poisoning. Patients should be considered for HBO treatment if they are symptomatic and have a HbCO level more than 25%. In many countries, including India, hyperbaric facilities are scarce and, in any case, there are great technical difficulties in the transfer and administration of HBO treatment to a severely burned patient.

Cyanide (CN) poisoning: Hydrogen cyanide causes tissue asphyxia by inhibition of cytochrome oxidase, which prevents mitochondrial O_2 consumption and arrests the tricarboxylic acid cycle. The only pathway left for adenosine triphosphate (ATP) production is anaerobic metabolism of pyruvate to lactate and consequently metabolic acidosis. Clinical symptoms vary with the concentration:

- 50 ppm—Headache, dizziness, tachycardia and tachypnea
- 100 ppm—Lethargy, seizures and respiratory failure.

Treatment is normally conservative but high CN levels and persisting metabolic acidosis should be treated with sodium thiosulfate (increases hepatic metabolism to inactive metabolites), sodium nitrites (provide methemoglobin, which combines with CN to form inactive cyanomethemoglobin) and dicobalt edetate (binds to CN to form an inactive complex).

C—Circulation

Intravenous (IV) access should be established with two large bore cannulas preferably placed through unburnt tissue. This is an opportunity to take blood for checking full blood count, urea and electrolytes, blood group and clotting screen. Peripheral circulation must be checked. Any deep or full thickness circumferential extremity burn can act as a tourniquet, especially once edema develops after fluid resuscitation. This may not occur until some hours after the burn. If there is any suspicion of decreased perfusion due to circumferential burn, the tissue must be released with escharotomies. Profound hypovolemia is not the normal initial response to a burn. If a patient is hypotensive then it is may be due to delayed presentation, cardiogenic dysfunction, or an occult source of blood loss (chest, abdomen, or pelvis).

D—Neurological Disability

All patients should be assessed for responsiveness with the Glasgow coma scale; they may be confused because of hypoxia or hypovolemia.

E—Exposure with Environment Control

The whole of a patient should be examined (including the back) to get an accurate estimate of the burn area and to check for any concomitant injuries. Burn patients, especially children, easily become hypothermic. This will lead to hypoperfusion and deepening of burn wounds. Patients should be covered and warmed as soon as possible.

F—Fluid Resuscitation

The resuscitation regimen should be determined and begun. This is based on the estimation of the burn area. A urinary catheter is mandatory in all adults with injuries covering more than 20% of TBSA to monitor urine output. Children's urine output can be monitored with external catchment devices or by weighing nappies provided the injury is less than 20% of total body area. In children the intraosseous route can be used for fluid administration if IV access cannot be obtained but should be replaced by IV lines as soon as possible.

Analgesia

Superficial burns can be extremely painful. All patients with large burns should receive IV morphine at a dose appropriate to body weight. This can be easily titrated against pain and respiratory depression. The need for further doses should be assessed within 30 minutes.

Assessment and Resuscitation

Assessment of Burn Area

Assessment of burn area tends to be done badly, even by those who are expert at it. There are three commonly used methods of estimating burn area, and each has a role in different scenarios. When calculating burn area, erythema should not be included. This may take a few hours to fade, so some overestimation is inevitable if the burn is estimated acutely.

Palmar surface: The surface area of a patient's palm (including fingers) is roughly 0.8% of TBSA. Palmar surface can be used to estimate relatively small burns (<15% of total surface area) or very large burns (>85%, when unburnt skin is counted). For medium-sized burns, it is inaccurate.

Wallace rule of nines: This is a good, quick way of estimating medium to large burns in adults. The body is divided into areas of 9%, and the total burn area can be calculated. It is not accurate in children.

by mansdocs.com

Lund and Browder chart: This chart, if used correctly, is the most accurate method. It compensates for the variation in body shape with age and therefore can give an accurate assessment of burns area in children.

It is important that all of the burn is exposed and assessed. During assessment, the environment should be kept warm, and small segments of skin exposed sequentially to reduce heat loss. Pigmented skin can be difficult to assess, and in such cases it may be necessary to remove all the loose epidermal layers to calculate burn size.

Resuscitation Regimens

Fluid losses from the injury must be replaced to maintain homeostasis. There is no ideal resuscitation regimen, and many are in use. All the fluid formulas are "only guidelines", and their success relies on adjusting the amount of resuscitation fluid against monitored physiological parameters. "The main aim of resuscitation is to maintain tissue perfusion to the zone of stasis to prevent the burn deepening." This is not easy, as too little fluid will cause hypoperfusion whereas too much will lead to edema that will cause tissue hypoxia. The greatest amount of fluid loss in burn patients is in the first 24 hours after injury. For the first 8–12 hours, there is a general shift of fluid from the intravascular to interstitial fluid compartments. This means that any fluid given during this time will rapidly leave the intravascular compartment. Colloids have no advantage over crystalloids in maintaining circulatory volume. Fast fluid boluses probably have little benefit, as a rapid rise in intravascular hydrostatic pressure will just drive more fluid out of the circulation. However, much protein is lost through the burn wound, so there is a need to replace this oncotic loss. Some resuscitation regimens introduce colloid after the first 8 hours, when the loss of fluid from the intravascular space is decreasing.

Burns covering more than 15% of TBSA in adults and more than 10% in children warrant formal resuscitation. Again these are guidelines, and experienced staff can exercise some discretion either way. The most commonly used resuscitation formula is the Parkland formula, a pure crystalloid formula. It has the advantage of being easy to calculate and the rate is titrated against urine output. This calculates the amount of fluid required in the first 24 hours. Children require maintenance fluid in addition to this.

The starting point for resuscitation is the time of injury, not the time of admission. Any fluid already given should be deducted from the calculated requirement.

At the end of 24 hours, colloid infusion is begun at a rate of 0.5 mL × [total burn surface area (%)] × [body weight (kg)], and maintenance crystalloid (usually dextrose-saline) is continued at a rate of 1.5 mL × (burn area) × (body weight). The end point to aim for is a urine output of 0.5–1.0 mL/kg/hr in adults and 1.0–1.5 mL/kg/hr in children.

High-tension electrical injuries require substantially more fluid [up to 9 mL × (burn area) × (body weight) in the first 24 hours] and a higher urine output (1.5–2 mL/kg/hr). Inhalational injuries also require more fluid.

Colloid use is controversial: some units introduce colloid after 8 hours, as the capillary leak begins to shut down whereas others wait until 24 hours. Fresh frozen plasma is often used.

The above regimens are merely guidelines to the probable amount of fluid required. This should be continuously adjusted according to urine output and other physiological parameters (pulse, blood pressure, and respiratory rate). Investigations at intervals of 4–6 hours are mandatory for monitoring a patient's resuscitation status. These include packed cell volume, plasma sodium, base excess and lactate.

Escharotomy and Fasciotomy

In circumferential full thickness burns to the extremities, chest or neck, escharotomy may be required, commonly required in flame burns. Less often this may be required in chest or neck circumferential burn to improve pulmonary compliance or prevent airway obstruction. Constriction occurs due to shrinkage and loss of elasticity in heat coagulated skin with associated intense underlying edema which develops progressively. Raised tissue, occluded blood vessels and necrosis develop if unrelieved. Escharotomy is an urgent procedure which should be carried out in the first few hours postburn.

Typical Incisions

- From the anterior axillary line down to the iliac crest, then proceeding down the lateral side of the leg to the lateral malleolus and along fifth metatarsal bone if necessary.
- This can be supplemented by an incision across the chest along the costal margins, along the sternum and toward the lateral clavicles if necessary (X-shaped escharotomy). The abdomen can be decompressed with a horizontal escharotomy along the superior border of the pubic bone.

by mansdocs.com

- Bilateral incisions down the anterior border of the sternocleidomastoid muscle relieves neck.
- Incision along third metacarpal bone, dorsal forearm and lateral humerus.
- If the legs are involved, escharotomies down the medial side of the leg give a better cosmetic result. However, they must be supplemented by lateral escharotomies if decompression is inadequate.

Fasciotomy

A compartment syndrome of the muscles may occur in electrical burns, deep flame burns and crush or burn injuries. Diagnose by clinical suspicion and compartment pressure measurement. Pressure monitoring is particularly useful in unconscious, intubated patients and in the proximal part of the limb in electrical injury. Escharotomy or fasciotomy is useful to identify and excise devitalized muscle.

Excision

Early tangential surgical excision and grafting remove the source of the inflammatory response and provide a barrier to infection. It has been shown to decrease pain, the number of operations required, blood loss, length of hospital stay and mortality rate, as well as achieving a better functional result. Excision and grafting should take place as soon as the patient is stable. Debridement and grafting will cause significant hemorrhage and hypothermia. The procedure should be stopped if the patient gets cold—it is often not possible to cover the patient up for surgery, as the good skin may be harvested to make grafts.

INTENSIVE CARE MANAGEMENT AND CONTROL OF INFECTION

Intensive Care Management

The goal in management of an acute burn is to limit the extent of the systemic insult. Intensive care management should not be seen as rescue for failed initial treatment but as a preventive measure in patients at high risk of organ failure. Intensive care units (ICUs) have the resources for improved monitoring and expertise in managing acute physiological changes. Intensive care management should not, however, become an obstacle to early aggressive surgical excision of the burn wound, which is associated with improved outcome.

Airway Burns

The term "inhalational injury" has been used to describe the aspiration of toxic products of combustion, but also more generally any pulmonary insult associated with a burn injury.

Patients with cutaneous burns are 2–3 times more likely to die if they also have lower airway burns. Death may be a direct result of lung injury but is usually due to the systemic consequences of such injury. It may be impossible to distinguish lung injury caused at the time of the burn directly to the lungs by a burn from injury due to the systemic consequences of the burn.

Diagnosis of lower airway burns is largely based on the patient's history and clinical examination. Clinicians should have a high index of suspicion of airway burns in patients with one or more of the warning signs. Special investigations will support clinical suspicion. However, severity of injury or prediction of outcome is not aided by additional tests.

The pathophysiology of airway burns is highly variable, depending on the environment of the burn and the incomplete products of combustion. The clinical manifestations are often delayed for the first few hours but are usually apparent by 24 hours. Airway debris—including secretions, mucosal slough, and smoke residue—can seriously compromise pulmonary function.

There is no specific treatment for airway burns other than ensuring adequate oxygenation and minimizing iatrogenic lung insult. Prophylactic corticosteroids or antibiotics have no role in treatment.

Control of the airway by endotracheal intubation is essential before transporting any patient with suspected airway burn. Rapid fluid administration with inevitable formation of edema may lead to life-threatening airway compromise if control of the airway is delayed. Endotracheal intubation before edema formation is far safer and simpler. Oxygen (100%) should be given until the risk of CO toxicity has been excluded, since high concentrations of oxygen will clear CO from the body more rapidly than atmospheric concentrations. Importantly, CO toxicity may result in a falsely elevated pulse oximetry saturation.

Airway burns are associated with a substantially increased requirement for fluid resuscitation. Reducing the fluid volume administered, to avoid fluid accumulation in the lung, results in a worse outcome. Invasive monitoring may be required to guide fluid administration,

by mansdocs.com

especially with failure to respond to increasing volumes of fluid. Adequate oxygen delivery to all the tissues of the body is essential to prevent multiorgan failure.

Aggressive airway toilet is essential. Diluted heparin and acetylcysteine nebulization may be helpful. Early surgical debridement, enteral feeding, mobilization of the patient, and early extubation are desirable. Antibiotics should be reserved for established infections and guided by regular microbiological surveillance.

Several ventilatory strategies have been proposed to improve outcome following airway burns. Adequate systemic oxygenation and minimizing further alveolar injury are the primary clinical objective. Prolonging survival will permit spontaneous lung recovery.

Intensive monitoring: The intensive care environment facilitates rapid, graded response to physiological disturbance. Frequent reassessment based on a range of clinical and monitored parameters should guide treatment. Fluid administration should not be guided by calculated fluid requirements alone. Failure to respond to treatment should trigger an escalation in the invasiveness of the monitoring.

Heart Failure

Myocardial dysfunction is a potential consequence of major burn injury. It has been attributed to a circulating myocardial depressant factor, primarily causing myocardial diastolic dysfunction. It may also be caused by myocardial edema. Administration of an inotropic agent is preferable to overloading a failing myocardium with large volumes of fluid.

However, the inotropic drug can produce vasoconstriction in the burn wound, reducing the viability of critically injured tissue. Inotropic drugs should not be used until adequate fluid resuscitation has been ensured (usually by invasive monitoring). Inotropic drugs that do not produce vasoconstriction (such as dopexamine or dobutamine) will preserve wound viability, providing they do not produce unacceptable hypotension.

Kidney Failure

Early renal failure after burn injury is usually due to delayed or inadequate fluid resuscitation, but it may also result from substantial muscle breakdown or hemolysis. Delayed renal failure is usually the consequence of sepsis and is often associated with other organ failure.

A reduced urine output, despite adequate fluid administration, is usually the first sign of acute renal failure.

This will be followed by a rise in serum creatinine and urea concentrations. Early renal support (hemodialysis or hemodiafiltration) will control serum electrolytes and accommodate the large volumes of nutritional supplementation required in a major burn.

Cerebral Failure

Hypoxic cerebral insults and closed head injuries are not uncommonly associated with burn injuries. Fluid administration for the burn injury will increase cerebral edema and intracranial pressure. Monitoring intracranial pressure may help in minimizing the adverse effects of trying to achieve two contradictory treatment goals.

Nutrition

Burn injury is associated with a considerable hypermetabolic response, mediated by the systemic response to the burn and related to the extent of the burn injury. The hypermetabolism may result in a resting energy expenditure increase in excesses of 100% of basal metabolic rate. Even small burns can be associated with hyperpyrexia directly due to hypermetabolism.

Only limited success has been achieved in reducing the hypermetabolic state, which may persist for many months.

Close attention to nutritional needs is critical to prevent protein breakdown, decreased wound healing, immune suppression, and an increase in infective complications.

Energy requirements are proportional to the size of the burn and should be met by enteral nutrition, and this should be established as soon as possible after the burn injury. Total parenteral nutrition is associated with immunosuppression, an increase in infective complications, and reduced survival. Glutamine, arginine, and omega-3 fatty acid supplementation may improve immunity and gut function.

INFECTION IN BURNS PATIENTS

After the initial resuscitation, up to 75% of mortality in burns patients is related to infection. Preventing infection, recognizing it when it occurs, and treating it successfully present considerable challenges. Infective pulmonary complications are now the most common types of infection seen in burns patients, but infection is common in many other sites. Several factors contribute to the high frequency and severity of infection at multiple sites in burns patients:

by mansdocs.com

- Destruction of the skin or mucosal surface barrier allows microbial access.
- Presence of necrotic tissue and serosanguinous exudate provides a medium to support growth of microorganisms.
- Invasive monitoring provides portals for bacterial entry.
- Impaired immune function allows microbial proliferation.

Deciding whether infection is present can be difficult. Burns patients have an inflammatory state from the injury itself that can mimic infection. Extensive microbial colonization of wounds makes interpretation of surface cultures difficult.

Patients may have open wounds and repeated episodes of infection over weeks. Excessive use of antibiotics will encourage the appearance of resistant colonizing organisms. A sensible approach is to limit antibiotic use to short courses of drugs with as narrow a spectrum of activity as is feasible.

PATHOGENESIS

The burn injury destroys surface microbes except Gram-positive organisms located in the depths of the sweat glands or hair follicles. Without prophylactic use of topical antimicrobial agents, the wound becomes colonized with large numbers of Gram-positive organisms within 48 hours. Gram-negative bacteria appear from 3 days to 21 days after the injury. Invasive fungal infection is seen later.

The microbiology reflects the hospital environment and varies from center to center. In general, there has been a change in the main infective organisms over time from beta-hemolytic streptococci to resistant Gram-negative organisms including *Pseudomonas*, resistant Gram-positive organisms, and fungi.

Preventing Invasive Wound Infection

One aim of initial wound management is to prevent invasive infection. To this end, aggressive surgery and the use of topical antimicrobial agents are effective. Topical antimicrobial treatment slows wound colonization and is of early use, before definitive surgery. A wide selection of agents is available: silver sulfadiazine is the most frequently used. Early closure of the burn wound by surgical techniques then lessens the surface area available for further microbial colonization and subsequent infection.

Prophylactic use of systemic antibiotics is controversial. Most agree that prophylactic penicillin against group A streptococcal sepsis is not indicated, and broad-spectrum antibiotics to cover wound manipulation are not required in patients with burns covering less than 40% of TBSA.

Diagnosing Invasive Wound Infection

Surface swabs and cultures cannot distinguish wound infection from colonization. Wound biopsy followed by histological examination and quantitative culture is the definitive method.

However, it is time-consuming and expensive, making it impractical as a routine diagnostic technique. Diagnosis of infection therefore relies heavily on clinical parameters, with the aid of blood, surface, or tissue cultures to identify likely pathogens.

TREATMENT

When invasive infection of a burn wound is suspected, empirical systemic antimicrobial treatment must be started. Topical treatment alone is not sufficient, as it does not effectively penetrate the eschar and damaged tissue. The choice of antibiotic depends on the predominant flora on the unit. This can be adjusted later depending on culture and sensitivity results of relevant specimens. Necrotic and heavily infected material must be removed by surgical excision.

Infection Control

Infection control measures help to minimize cross infection between patients and acquisition of nosocomial pathogens [such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multiresistant Gram-negative bacteria]. Strict isolation of every patient is impractical, but universal precautions are an absolute necessity.

BURNS IN THE DEVELOPING WORLD AND BURN DISASTERS

Problems in Management

Burn management in developing countries is riddled with difficulties. Lack of government initiative and low literacy rates preclude effective prevention programs. Many uneducated households are fraught with superstition, taboos, weird religious rituals, and faith in alternative systems of "medicine", which complicate management.

by mansdocs.com

Most burn centers are situated in large cities and are inadequate for the high incidence of injuries. Resuscitation is often delayed as patients have to travel long distances and transport facilities are poor. Many burn centers are also plagued with lack of resources, lack of operating time, and shortage of blood. Often there are no dedicated burn surgeons, and general surgeons without formal training are involved in burn care. Burn nursing is also not a recognized concept. These conditions make excisional surgery impossible for a large percentage of patients. There is generally no coordination between district hospitals and tertiary burn centers.

Strategies for Effective Burn Care in Developing Countries

The approach to burn management has to be radically different from that in western countries.

Prevention Programs

Prevention programs should be directed at behavioral and environmental changes which can be easily adopted into lifestyle. The programs need to be executed with patience, persistence, and precision, targeting high-risk groups.

Depending on the population of the country, burns prevention could be a national program. This can ensure sufficient funds are available and lead to proper coordination of district, regional and tertiary care centers. It could also provide for compulsory reporting of all burn admissions to a central registry, and these data could be used to evaluate strategies and prevention programs. There should be adequate provision by law to set manufacturing standards for heating and electrical equipment, fire safety standards for high-rise buildings, and procedures for storage and transportation of hazardous materials, explosive chemicals and firecrackers. A national body of burn professionals should be constituted to educate all health care staff involved in burn care.

Providing Treatment

To provide optimal burn care to a large population with limited resources, it is imperative to strengthen the existing infrastructure. A few regional burn centers should be developed to provide tertiary management and training to burn care staff.

General surgeons working in district hospitals should form the nucleus of the burn care service and decide on referral procedures.

If it is not possible to keep referred patients at burn centers for 6–8 weeks of treatment, they can be discharged after 2 or 3 weeks of stabilization. Such patients can then be treated at district hospitals or at home with the help of primary health centers. Thus, primary health centers can act as liaison between burn patients and district hospitals. The incidence of burn wound septicemia with domiciliary treatment is remarkably low. These patients can be readmitted as necessary for blood transfusions, treating septicemia, and skin grafting.

Certain well tested and cost-effective treatment procedures need to be adopted to conserve resources: these include using Parkland formula for resuscitation, pursuing conservative burn wound management, and using amnion as a biological dressing.

Burn Disasters

A disaster is a situation that is unpredictable, massive, and poses an immediate threat to public health. A burn disaster is "an event resulting in mass burn casualties and severe loss of human lives and material from a known thermal agent". Disasters normally exceed the resources of local health care facilities.

Disaster management involves:

- Coordinating the activities of various health disciplines to prevent disasters
- Providing an immediate response to a disaster
- Helping in rehabilitation of victims.

Disaster Plan

An organized disaster plan can reduce loss of property, social disruption and suffering. A disaster plan should be especifically tailored for a particular region and nature of fire disaster. Ultimately, a coordinated system must be developed that includes medical and public safety organizations, law and order agencies, and transport agencies.

The communication lines from the central command should be fast and multilingual. It should be able to advise workers at the disaster site, direct transport agencies, and simultaneously relay the information to surrounding hospitals. All the regional and distant hospitals must be incorporated in a multitier system as the number of cases may overwhelm local facilities.

Hospitals play a pivotal role in providing trained staff. All doctors and nurses, irrespective of their specialties and whether they are included in the plan, should be educated about the basics of burn care. With a burn specialist at the core, the hospital disaster management team also

by mansdocs.com

includes a respiratory physician and an anesthetist. There should be prompt and judicious deployment of staff. Teams of psychologists should manage panic among disaster victims and their relatives both at the disaster site and at hospitals. Accurate triage by clinicians experienced in burns must guide the flow of patients from the site to the inner circle of health care facilities (primary and secondary care hospitals) and then to the outer circle (tertiary care hospitals and burn centers).

Transportation needs are guided by the number of victims, their condition, the nature of the fire disaster and geographical considerations. Possible modes of transport include ambulances, local transport vehicles, military vehicles, helicopters, fixed-wing aircraft and rescue boats.

Managing a Disaster

Immediate care is provided by people present at the scene of the disaster, who may be survivors or passersby. These first responders are later guided by trained health care workers who arrive at the site. On site management includes first aid, patient triage, and ambulance staging with a basic aim of maximal use of resources.

Triage: Triage is the cornerstone of effective burn disaster management and is done at the disaster site by staff with knowledge of burn treatment. Triage takes into consideration the total number of patients, bed availability, and transportation capacity.

Triage should be prognostic, and patients should be categorized on the basis of age, extent of burns, site of burns and presence of inhalational injury:

- Group I—Minor burns (< 10% of total surface area in children, < 20% in adults) to noncritical areas; Assigned to—outpatient care, dressing, tetanus prophylaxis
- Group II—Minor burns to critical sites (face, hands, genitalia); Assigned to—short hospital stay, special wound care or operation
- Group III—Major burns (20–60%); Assigned to—admission to burn unit, IV resuscitation
- Group IV—Extensive burns (> 60%); Assigned to—lower priority for transfer
- Group V—Minor burns with inhalational injury or associated injury; Assigned to—oxygen, intubation, transfer to ICU.

The patients in groups III and V are evacuated first, followed by group IV. Group II cases are evacuated at the end. Group I cases are either discharged after first aid or asked to make their own way to the nearest primary care center.

FURTHER TREATMENT

Initial care is in the line of ABC of resuscitation. An adequate airway and respiration must be ensured. All patients except those with minor burns must receive fluid resuscitation based on a simple formula. Wounds should be covered with a sterile sheet until they are dressed. Dressings should be simple, with only antimicrobial pads and Gamgee tissue. Effort should be made to detect and treat associated injuries.

Secondary triage may also be done at this time. If necessary, seriously injured patients can be sent to centers of higher level while less serious patients who reach the tertiary centers are referred back to primary care centers. The success of such a plan lies in accurate triage at every level, so that all centers are used optimally and best possible treatment is delivered to all according to the severity of injury with minimum delay.

by mansdocs.com

CHAPTER

60

Diabetic Ketoacidosis

DK Singh

Diabetes ketoacidosis (DKA) is an emergency characterized by hyperglycemia, ketonemia, ketonuria, metabolic acidosis and dehydration. It is a complication of type 1 diabetes mellitus. It may be first presentation of type 1 diabetes mellitus, a state of absolute insulin deficiency. In those who are already known to have type 1 diabetes mellitus and are on therapy, it is due to a relative insulin deficiency either arising due to discontinuation of therapy, or increased physiologic demand.

While DKA is a serious life-threatening condition encountered in the intensive care unit (ICU), if managed promptly and precisely, is reversible. A typical scenario is that the patient is rushed to the ICU in either a gasping, semicomatose state or totally unconscious with shallow respiration. Patient is often dehydrated with poor skin turgor.

ETIOPATHOGENESIS

Diabetes ketoacidosis is precipitated by insulin deficiency. Insulin deficiency leads to reduced penetration of glucose in the cells as well as increased gluconeogenesis and glycogenolysis in the liver. This leads to hyperglycemia as well as increased free fatty acids due to lipolysis. Hyperglycemia leads to increased intravascular osmolarity, polyuria, and dehydration. Because of the high osmolarity leading to osmotic diuresis, the patient has a fluid deficit of 4–6 liters. Excess free fatty acids which are end products of gluconeogenesis metabolize to form ketone bodies (β-hydroxylbutyrate and acetoacetate), leading to ketosis. Accumulation of excess ketones leads to high anion gap metabolic acidosis. Initially, the bicarbonate buffers act to counter the acidic pH; however, after the buffers are exhausted, additional compensatory mechanisms start to act.

Patient with DKA presents with manifestations of dehydration (dry tongue, dry mucosa, poor skin turgor, tachycardia, and hypotension) and acidosis (hyperventilation). Sometimes in extreme cases, due to dehydration and low CO_2, there is development of cerebral edema, leading to coma. Immediate assessment in emergency rooms reveals very high blood sugar levels (usually higher than 300 mg/dL), and positive urinary ketones. Arterial blood gases will confirm metabolic acidosis with a high anion gap. While management is initiated as soon as DKA is confirmed, additional investigations are ordered to look for any focus of infection, which may be precipitating cause of DKA (complete blood count, urinary cultures and chest radiology), or for comorbidities such as coronary artery disease (electrocardiography).

DIAGNOSIS

Following are the diagnostic features of DKA:

Clinically

- Hyperventilation (often Kussmaul's respiration)
- Ketotic odor in breath
- Tachycardia
- Patient restless or semicomatose.

Blood

- High blood sugar (>300 mg%)

by mansdocs.com

- Acidosis (pH < 7.3)
- Sometimes impaired electrolytes.

Urine

- Ketone bodies present.

DIFFERENTIAL DIAGNOSIS

Clinically, the condition might sometimes mimic myocardial infarction or urinary tract infection. They must be ruled out by thorough physical examination and other investigations. However, a search for any underlying infectious foci should always be made.

Diabetic ketoacidosis has to be differentiated with other forms of ketoses and diabetic emergencies.

Diabetes ketoacidosis has a conglomeration of high blood sugar, acidosis in blood and presence of ketones in blood or urine.

Hyperosmolar nonketotic state has to be distinguished from DKA as the former condition is more common in type 2 diabetics in contrast to DKA. The plasma osmolarity in hyperosmolar nonketotic state is more than 320 mOsm/kg. The ketosis and acidosis are not as high as in DKA. Alcoholic ketosis mimics DKA but blood sugar level is normal. Ketosis from starvation again has similarity to DKA but the sugar level is normal. Acidosis can result from a myriad of other causes but other signs peculiar to DKA mentioned above will be absent.

MANAGEMENT

Identification and correction of the underlying cause that precipitated the event is most important.

Ideally, the patient suspected or diagnosed of diabetic ketoacidosis should be immediately shifted to ICU and managed there, because in DKA the physiological derangements deteriorate or improve at a fast rate. Therefore, close monitoring and prompt action are necessary.

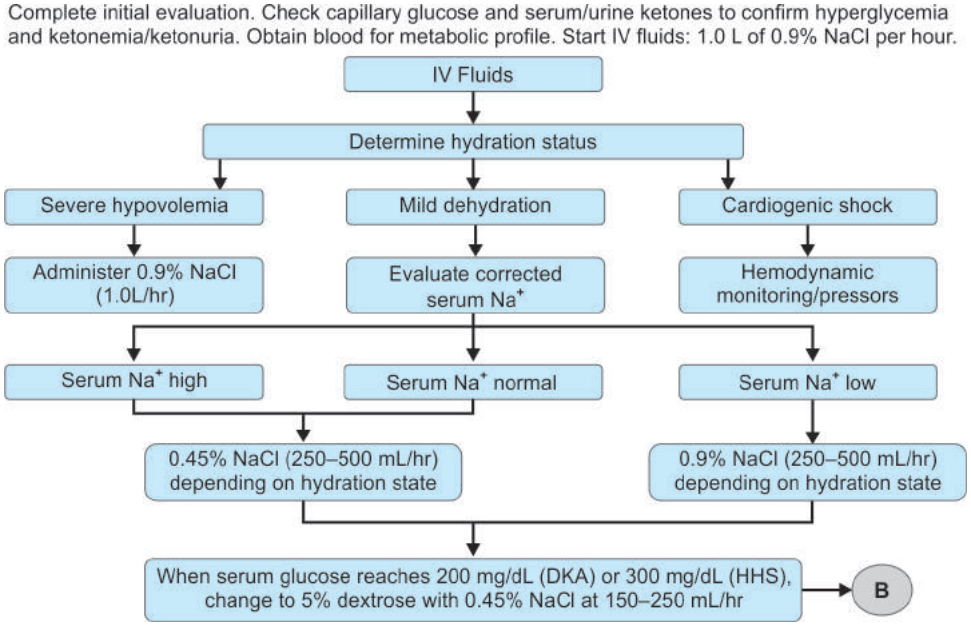
The goal of treatment of DKA is:

- Prompt correction of hypovolemia
- Gradual reduction of high sugar levels
- Optimization of electrolytes
- Resolution of ketosis
- Treatment of underlying infectious condition, if any.

Fluid correction is the first-line of management. It should be done by infusion of 0.9% saline according to the degree of dehydration. If the patient is in ICU, a central venous catheter should be inserted and fluid resuscitations should be guided by central venous pressure (CVP) valve. Maintain CVP between 8 cm and 10 cm H2C. Otherwise, any signs of dehydration indicate significant fluid loss and at least 3–4 liters of saline must be infused (Flowchart 1).

Initiation of insulin for management of hyperglycemia is next line in management. Reduction of sugar levels is achieved by insulin infusion. Various regimes have been suggested for this (detailed discussion is outside the scope of this chapter). However, it must be kept in

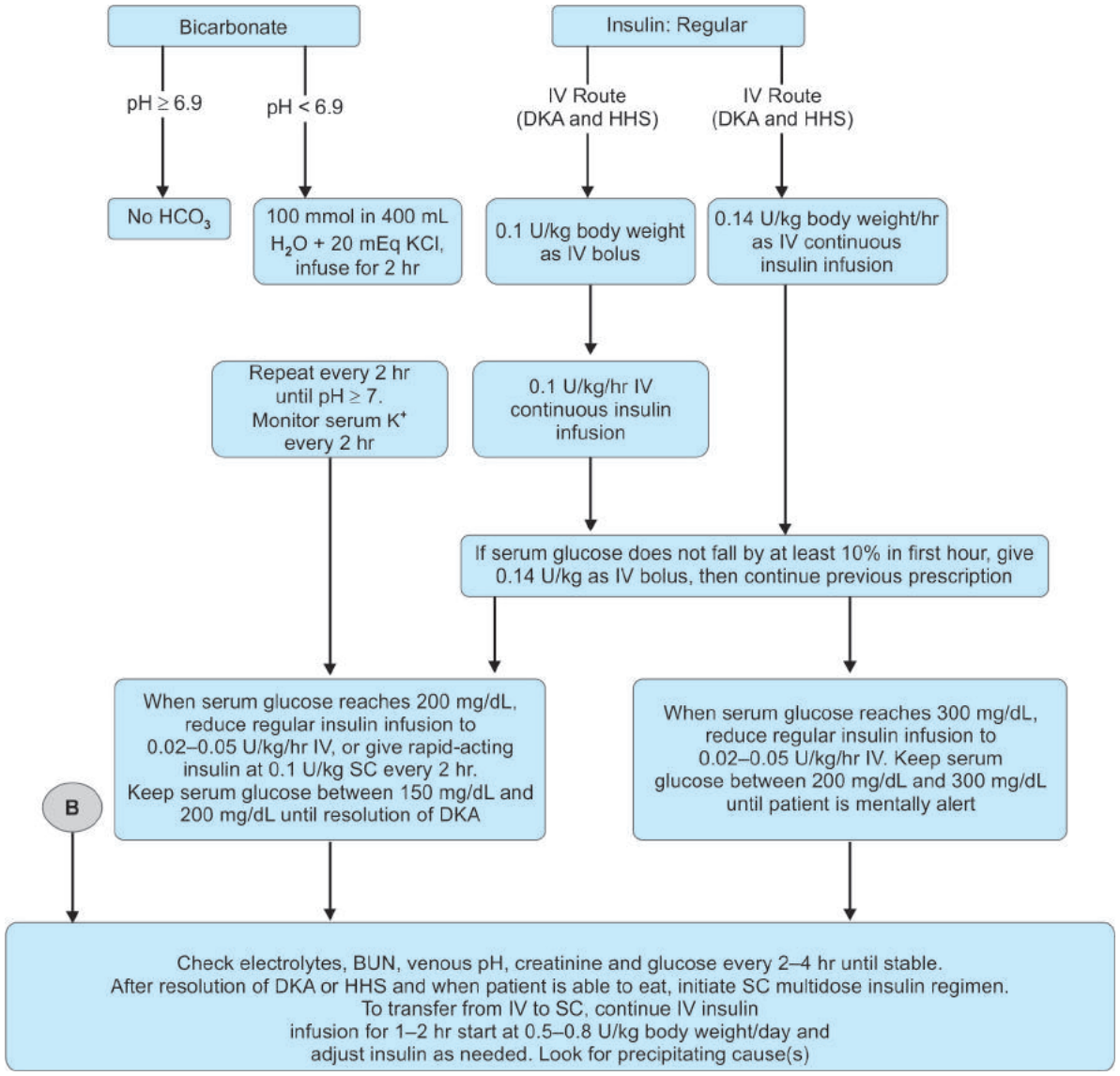
Flowchart 1: Fluid management in diabetes ketoacidosis.



(DKA: Diabetes ketoacidosis; HHS: Hyperosmolar hyperglycemic state; IV: Intravenous).

by mansdocs.com

Flowchart 2: Management of acidosis and hyperglycemia in diabetes ketoacidosis.



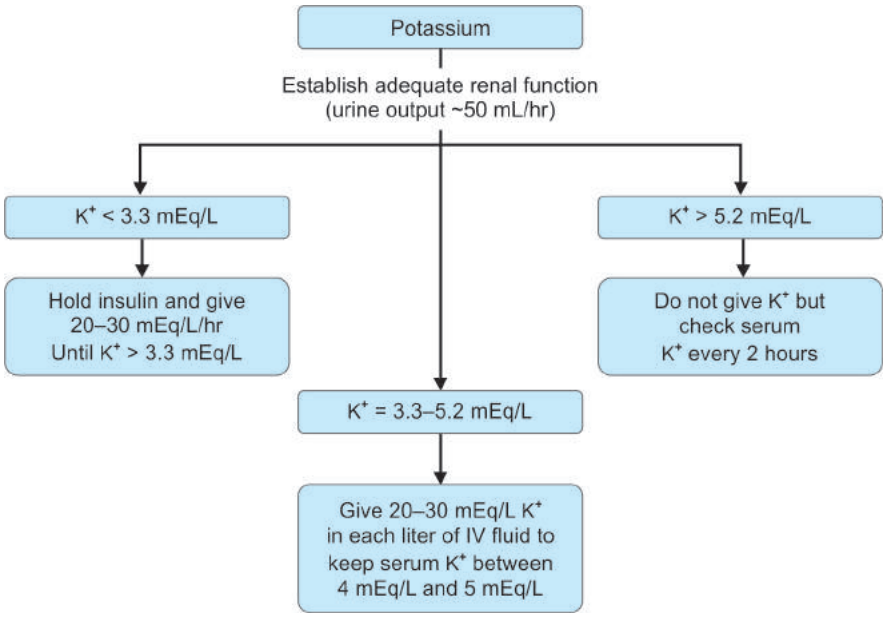
(BUN: Blood urea nitrogen; DKA: Diabetes ketoacidosis; HHS: Hyperosmolar hyperglycemic state; IM: Intramuscular; IV: Intravenous; SC: Subcutaneous).

mind that there should not be a rapid correction in blood sugar levels. They must be gradually brought down until they come to lie in a range of 275–300 mg%. The high production of ketone bodies is also corrected simultaneously with insulin infusion (Flowchart 2).

Electrolyte correction—serum electrolytes should be closely monitored. Potassium derangement is common, partly because of loss in urine and partly because of insulin infusion. Because of this reason, a close monitoring for arrhythmias also has to be done. Sodium bicarbonate should be used for acidosis correction only when it is severe and pH is below 6.9. If there is evidence of any underlying infection, appropriate antibiotic cover should be given (Flowchart 3).

by mansdocs.com

Flowchart 3: Management of potassium abnormalities in diabetes ketoacidosis.



With restoration of hydration with fluid management, and reversal of hyperglycemia with insulin infusion, ketosis reverses. If pH is low, bicarbonate infusion may be required. Insulin infusion is continued till normalization of pH (resolution of metabolic acidosis). Disappearance of urinary ketones usually takes longer.

Once DKA resolves, patient needs to be shifted to subcutaneous insulin regimen before shifting.

by mansdocs.com

CHAPTER

61

Oncological Emergencies

Sheila Nainan Myatra, Amol Kothekar

INTRODUCTION

Oncological emergencies form an important reason for admission to intensive care unit (ICU) in cancer patients. Most of the oncological emergencies occur during the initial evaluation and treatment of cancer. However, a few cases like spontaneous tumor lysis in an undiagnosed hematolymphoid malignancy or superior vena cava (SVC) syndrome may present as an emergency even before diagnosis. A thorough understanding of these complex conditions is required for the appropriate management of these conditions, especially for those physicians, who do not routinely treat cancer patients in ICU.

Common oncological emergencies seen in clinical practice are:

- Tumor lysis syndrome (TLS)
- Hypercalcemia
- Superior vena cava syndrome
- Spinal cord compression

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is usually seen during treatment of a rapidly proliferating neoplasm. It occurs due to rapid death of predominantly malignant cells. The rapid cell lysis results in release of intracellular products into the systemic circulation which occurs more rapidly than the body can eliminate. This results in metabolic derangement characterized by the development of hyperphosphatemia, hyperkalemia, hyperuricemia, and hypocalcemia which can lead to acute oliguric renal failure and other complications.

Conditions Associated with Tumor Lysis Syndrome

Tumor lysis syndrome is most commonly seen with cytotoxic chemotherapy treatment in rapidly dividing myeloproliferative and lymphoproliferative disorders, classically the high grade lymphomas and acute leukemias. It is less commonly seen in chronic leukemias and low grade lymphomas. Solid tumors rarely produce TLS, but carry a higher mortality, probably because of delayed presentation and delayed recognition. While most often associated with chemotherapy, TLS may sometimes present spontaneously (even before treatment) due to tissue ischemia causing tumor cell lysis. It may also occur in patients treated with a variety of other oncological therapies (Table 1).

Table 1: Conditions associated with tumor lysis syndrome.

Hematologic Disease	*Solid Tumors*	*Therapies*
• Acute leukemias	• Breast cancer	• Corticosteroids
• High-grade NHL	• Lung cancer	• Intrathecal methotrexate
• Chronic leukemias	• Germ cell cancer	• Tamoxifen
• Other NHL	• Soft tissue sarcoma	• Immunotherapy
	• Ovarian cancer	• Rituximab
	• Thymoma	• Total body irradiation
	• Vulvar cancer	
	• Medulloblastoma	
	• Metastatic melanoma	

(NHL: Non-Hodgkin lymphoma).

by mansdocs.com



Fig. 1: Oxidation of nucleotide precursors into uric acid.

Risk Factors for Tumor Lysis Syndrome

- Lymphoproliferative malignancy
- Bulky chemosensitive disease
- High serum urate level
- Elevated white blood cell count
- Presence of volume depletion
- Pre-existing renal dysfunction

In-hospital mortality of TLS is reported as approximately 7%. Acute renal injury at ICU admission increases the hospital mortality to 10 times. Usual cause of death in TLS is due to severe electrolyte abnormalities especially hyperkalemia or hypocalcemia and renal failure.

Pathophysiology of Tumor Lysis Syndrome

Hyperuricemia: It is the single most important clinical finding in patients with TLS who develop acute renal failure (ARF). Uric acid is the end-product of purine metabolism in humans. It is produced in the liver by the oxidation of xanthine and hypoxanthine. Uric acid has a pH of 5.6 and is 98% ionized at the physiologic pH. However, in the renal tubules and particularly in the collecting ducts where the pH approaches 5.0, uric acid becomes progressively less soluble and ionized (Fig. 1). Acute uric acid nephropathy can result secondary to crystal deposition in the distal tubules and collecting ducts.

Hyperkalemia: It is a frequent metabolic abnormality usually presenting within 12–48 hours after chemotherapy. This results from the rapid release of intracellular potassium. The most significant effect is cardiac arrhythmias, though neuromuscular abnormalities may also present.

Hyperphosphatemia/Hypocalcemia: Release of large amounts of tumor cell cytoplasm into the circulation leads to hyperphosphatemia. Hypocalcemia usually accompanies it; a result secondary to the effect of hyperphosphatemia on osteoclasts causing bone resorption and the formation of calcium phosphate complexes. These complexes can precipitate in the renal parenchyma or collecting ducts, leading to ARF.

Pathophysiology of Acute Renal Failure

Acute renal failure is a dreadful complication of TLS associated with high mortality and morbidity.

There are two different mechanisms proposed for ARF:

1. *Classical crystal-dependent mechanism*: Renal failure occurs due to renal tubular obstruction from precipitation of uric acid crystals (acidic urine) and calcium phosphate crystals (alkaline urine).
2. *Crystal-independent mechanism*: High levels of uric acid cause renal vasoconstriction, pro-oxidative and proinflammatory effects and antiangiogenesis.

Diagnosis of Tumor Lysis Syndrome

There are no symptoms specifically attributed to TLS. High level of suspicion and frequent monitoring of electrolytes and uric acid level are essential.

Cairo and Bishop have divided TLS into laboratory TLS and clinical TLS as follows.

Laboratory tumor lysis syndrome (LTLS): It is defined as fulfilment of following two or more criteria within a period of 3 days before or 7 days after the initiation of chemotherapy.

- Serum uric acid more than 8 mg/dL or 25% increase from baseline
- Serum potassium more than or equal to 6 mM or 25% increase from baseline
- Phosphorus more than or equal to 6.5 mg/dL (2.1 mM) for children or more than or equal to 4.5 mg/dL (1.45 mM) for adults or 25% increase from baseline
- Calcium less than or equal to 7.0 mg/dL (1.75 mM) or 25% decrease from baseline.

Clinical tumor lysis syndrome (CTLS): When LTLS is complicated by one of the following, it is considered as CTLS.

- Rise in serum creatinine to more than 1.5 times the upper limit of normal
- Incidence of cardiac arrhythmias or sudden death
- Seizure which cannot be attributed to a therapeutic agent.

Monitoring Parameters

Uric acid and electrolyte measurements should be done frequently in patients with high tumor burden, especially if profound response to chemotherapy is anticipated. Serum lactate dehydrogenase (LDH) more than 1500 U/L or hyperuricemia usually correlates with high tumor burden.

by mansdocs.com

Apart from vital parameters and intake output, renal functions [uric acid, creatinine and BUN (blood urea nitrogen)] and electrolytes (Na, K, Ca and PO_4) should be monitored frequently. LDH can also be used as a marker for response to therapy.

Treatment of Tumor Lysis Syndrome

Preventive strategy with aggressive hydration and antihyperuricemic therapy of TLS is the best treatment. Same therapy principles of hydration and antihyperuricemic therapy are used for treatment of established TLS.

Hydration

Usual prescription is hypotonic or isotonic saline up to 4 mL/kg/hr or 3 L/m^2/day. Patient's baseline electrolytes, cardiac function and fluid status should be taken into consideration. Urine output should be maintained within a range of 80–100 mL/m^2/hr (4–6 mL/kg/hr if <10 kg). Urine-specific gravity should be maintained at less than 1.010. Loop diuretics (frusemide) may be considered if urine output does not increase even after adequate hydration. However, caution is exercised in prescribing diuretics in patient with hypovolemia or obstructive uropathy.

Osmotic diuretic like mannitol (200–500 mg/kg) may also be considered. Caution should be exercised since mannitol with intravenous (IV) fluids may cause fluid overload.

Antihyperuricemic Therapy

Allopurinol: It is a xanthine oxidase inhibitor. It acts by blocking conversion of hypoxanthine and xanthine to uric acid. At physiologic pH, hypoxanthine is most soluble, followed by uric acid, and xanthine is least soluble. Hence, use of allopurinol may lead to formation of xanthine crystals in kidney.

Also, allopurinol does not act on pre-existing uric acid. Hence, it has to be given 2–3 days before the initiation of cytotoxic therapy. Dose of allopurinol is 300 mg/m^2/day. It is usually started at dose of 600 mg/day orally if uric acid is less than 8 mg/dL.

Dose of allopurinol should be reduced in renal failure and also in patients receiving chemotherapy agents like 6-mercaptopurine, 6-thioguanine and azathioprine.

Rasburicase: It is a recombinant urate oxidase which is genetically absent in humans. Its advantages over allopurinol are absence of clinically relevant drug–drug interactions and no need of dose adjustment in renal or hepatic dysfunctions. However, cost is the major issue for its use.

Usual dose is 0.20 mg/kg/day IV over 30 minutes given for up to 3 days.

Rasburicase vesus Allopurinol: American Society of Clinical Oncology (2008) guidelines recommend the use of hydration for all and prophylactic rasburicase in high risk, allopurinol or rasburicase for intermediate risk and clinical judgment and monitoring for patients who are at low risk for TLS.

However, evidence suggests that even though Rasburicase reduces serum uric acid, there is no benefit in terms of mortality or renal failure.

No urine alkalinization: Traditionally, urine alkalinization targeted to urine pH of more than eight was recommended as prophylaxis and treatment of TLS. Proposed benefit was increased solubility of uric acid in alkaline urine since uric acid has a pKa of 5.4. Since allopurinol does not reduce existing uric acid levels, this was the proposed mechanism to enhance excretion of uric acid.

Rasburicase oxidizes uric acid to allantoin which does not require alkalinization of urine. Other problems of alkalinization are precipitation of calcium phosphate crystals in renal tubules. It also causes hypocalcemia, and decreased phosphate excretion. Hence, alkalinization is not currently recommended because of the risk of decreasing ionized calcium concentrations, decreasing phosphate excretion, and increasing serum phosphate concentrations.

Other Supportive Therapies

Treatment of hyperkalemia: Intravenous calcium infusion rapidly reverses effects of hyperkalemia on heart. It should be reserved for life-threatening arrhythmias due to hyperkalemia. Dose is 100–200 mg/kg of calcium gluconate. Since calcium never reduces serum K^+ levels, other measures to treat hyperkalemia should be started simultaneously.

Other measures include inhaled Beta2-agonist like salbutamol or albuterol, intravenous glucose insulin drip, and potassium-binding resins like sodium polystyrene sulfonate. Dose of glucose insulin drip is 0.1 U/kg of regular insulin and 2 mL/kg of 25% dextrose. Patient's blood sugar should be monitored frequently. Dose of sodium polystyrene sulfonate is 1 g/kg with 50% sorbitol given in 3-4 divided doses orally. If patient cannot tolerate oral regimen, it can be given as retention enema.

by mansdocs.com

Sodium bicarbonate can be given when hyperkalemia is associated with metabolic acidosis with pH less than 7.2. Dose of $NaHCO_3$ is 1-2 mEq/kg IV.

Life-threatening hypocalcemia: Calcium gluconate 50–100 mg/kg.

Hyperphosphatemia: Aluminum hydroxide, 50–150 mg/kg/day in four divided doses, is given enterally.

Life-threatening hyperkalemia and hyperphosphatemia, resistant to medical management, should be treated with hemodialysis.

Role of hemodialysis: Acute renal failure in TLS increases mortality and morbidity. Indications of hemodialysis are quite similar to other causes of renal failure.

A few of the indications of hemodialysis are listed below:

- Volume overload,
- Uric acid more than 10 mg/dL despite rasburicase
- Hyperkalemia resistant to medical management
- Hyperphosphatemia resistant to medical management
- Acute renal failure
- Significant uremia.

General consensus is to start hemodialysis as soon as possible whenever indicated rather than delaying it to prevent a potentially reversible condition into an irreversible one.

Tumor lysis syndrome is a true oncological emergency leading to metabolic derangements that can lead to ARF, cardiac arrhythmias, seizures, tetany and even sudden death. Thus, it is important to recognize patients at an increased risk and initiate preventive therapy in a timely manner. However, when TLS arises unexpectedly or if prophylactic measures are not effective in preventing symptomatology, early recognition and management are essential to help prevent morbidity and mortality associated with this syndrome.

HYPERCALCEMIA

Hypercalcemia is seen in up to 10% of cancer patient population. Malignancies most commonly associated with hypocalcemia are breast, bronchus, and myeloma. It is also commonly seen with lymphoma and renal cell carcinoma. Occasionally, patient may present with hypocalcemia before diagnosis of a malignancy. Hypercalcemia of malignancy is usually seen in advanced malignancies and outcome is poor unless specific anticancer therapy option is available.

Etiopathogenesis

Parathyroid hormone-related peptide: It is the most common mechanism (80%) of hypercalcemia (called humoral hypercalcemia of malignancy). It is commonly seen in squamous tumors of lung, esophagus, head and neck, and cervix. PTHrP shares 13 amino acid sequence at N-terminal with native parathyroid hormone (PTH). This similarity explains humoral effects similar to PTH.

Vitamin D-linked Hypercalcemia: This is second most common (15%) mechanism of hypercalcemia. Normally, hypercalcemia leads to decreased production of $1,25(OH)_2D_3$ the active metabolite of vitamin D, at proximal convoluted tubules. However, many lymphoma patients exhibit abnormal vitamin D metabolism leading to increased $1,25(OH)_2D_3$ levels.

Osteoclast-activating factors: Multiple myeloma patients are prone for local osteolysis leading to bone resorption, osteopenia, and hypercalcemia. IL-1, IL-6, IL-11, PTHrP, hepatocyte growth factor, tumor necrosis factor, etc., are implicated for osteolysis, collectively known as osteoclast-activating factors. This mechanism is also responsible for hypercalcemia in breast cancer and lymphomas. Prostate cancer has high predilection for bone metastases but is rarely associated with hypercalcemia. This indicates that hypercalcemia occurs due to cytokine production by tumor rather than due to bone metastasis per se. This implicates cytokine production by tumor as cause of hypercalcemia rather than bone metastasis per se.

Diagnosis

Presenting symptoms of hypercalcemia, for example, anorexia, weakness, fatigue, nausea and vomiting are nonspecific and are many times confused with symptoms of underlying disease or chemotherapy. Some patients complain bone pain related to bone metastasis and osteoclastic activity. Polyuria and dehydration reflect hypercalcemia-induced dieresis. Confusion and drowsiness are usually seen at moderate to severe levels of hypercalcemia.

No single symptom can rule in or out hypercalcemia.

Diagnosis of hypercalcemia relies mainly on serum total and ionized calcium levels.

Level of chloride may differentiate between hypercalcemia due to malignancy and primary hyperparathyroidism. Former has serum chloride levels less than 100 mEq/L and later has mild hyperchloremic metabolic acidosis with chloride more than 103 mEq/L. However, this distinction is unreliable in patients with deranged renal function.

by mansdocs.com

Grading Hypercalcemia of Malignancy

Mild hypercalcemia: Asymptomatic patients with serum calcium level less than 3.0 mmol/L (12 mg/dL).

Moderate hypercalcemia: Asymptomatic patients with serum calcium of 3.0–3.5 mmol/L (12-14 mg/dL). These patients may deteriorate to severe hypercalcemia.

Severe hypercalcemia: Presence of symptoms attributable to hypercalcemia or serum calcium more than 3.5 mmol/L (14 mg/dL). These patients require urgent treatment.

In patients with hypoalbuminemia, serum calcium levels should be corrected for albumin.

The rate of increase in calcium level determines the symptomatology rather than absolute calcium level. Hence, severity of symptoms does not necessarily correlate with serum calcium level.

Electrocardiograph (ECG) changes in hypercalcemia: Hypercalcemia reduces automaticity and shortens refractory period. There is increased risk of arrhythmias. Also, atrioventricular blocks may occur due to prolonged PR interval.

Treatment

As previously mentioned, severe hypercalcemia should be treated only when treatment options are available for underlying malignancy. In fact, central nervous system (CNS) depression in hypercalcemia reduces suffering of advanced malignancy.

Treatment Principles

It can be divided into four components in order of priority.

1. Circulatory volume restoration and expansion
2. Therapy to target excretion of calcium (calciuretic therapy)
3. Therapy to prevent bone resorption (antiresorptive therapy)
4. Antitumor therapy for disease control.

Circulatory volume restoration and expansion: It is first and foremost therapy. Hypercalcaemic patients have dehydration and intravascular volume loss. This occurs due to poor oral intake because of nausea and vomiting; and polyuria and diuresis due to hypercalcemia. Fluid hydration with normal saline should be started immediately. Patient should receive 250–500 mL/hr till euvolemia is achieved. After that, 100–150 mL/hr IV should be infused. Fluid should be targeted to urine output of 100–150 mL/hr, taking into consideration patient's volume status. Patient's body weight, cardiac function, preload, and urine output should be taken into account for further titration of fluid therapy.

Therapy to target excretion of calcium (calciuretic therapy): Intravascular hydration causes excretion of calcium in urine. Furosemide increases calciuria by 30%. Since furosemide causes water and sodium loss, it prevents fluid overload in high risk patients and allows clinician to give more saline to cause further calciuria.

Furosemide should be strictly avoided in patients with intravascular hypovolemia. In this patient population, it will be counterproductive due to proximal tubular sodium and calcium resorption. Usual dose of furosemide is 20–40 mg IV.

Calcitonin: It is a natural antagonist of parathormone. It inhibits calcium reabsorption in the distal tubules and inhibits osteoclastic bone resorption. Calcitonin also requires adequate intravascular volume status to achieve calciuria. It is usually given for severe hypercalcemia (18 mg/dL). Dose of calcitonin is 4–8 IU/kg subcutaneous (SC) or IV given every 12 hours. It has rapid onset of action, acting immediately with IV dose and within 15 minutes with SC. Elimination half-life is up to 90 minutes but apparent biological half-life is said to be several hours.

Therapy to prevent bone resorption (Antiresorptive therapy)–Bisphosphonates: The bisphosphonates are structural analogs to pyrophosphate. They prevent osteoclastic bone resorption by inducing apoptosis in osteoclasts. They have poor oral bioavailability, mandating IV injections. They are prescribed for moderate and severe hypercalcemia with serum calcium more than 12 mg/dL. Usual dose is zoledronic acid 4 mg over 15 minutes or pamidronate 90 mg over 90 minutes. Up to 30% of patients experience low-grade pyrexia, bone pain, and myalgias known as first-dose effect. Bisphosphonates dose should be reduced and injections should be given more slowly in patients with renal impairment.

Agents like mithramycin or gallium nitrate are rarely used in current clinical practice.

Antitumor terapy for disease control: It is of least priority in ICU. As mentioned above, long-term prognosis is very poor if antitumor therapy cannot be planned. So, patient should be treated for hypocalcemia only if cancer treatment options are available. However, in ICU, cancer treatment is not a priority.

Miscellaneous therapy: In many hematolymphoid malignancies, glucocorticosteroids are given as part of

by mansdocs.com

chemotherapy regimen. They may reduce production of tumor factors responsible for hypercalcemia. Since glucocorticoids also block absorption of calcium from the gut, they might be useful for patients with vitamin D–mediated hypercalcemia. However, there is no strong evidence to support use of glucocorticoids.

Advice on Discharge

Patients should be encouraged to mobilize themselves since immobilization may predispose them to hypercalcemia. Patients are advised to take fluids up to 2–3 L/day. Patients should be educated about symptoms of hypercalcemia and to seek medical advice if symptoms occur.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava is a central vein in mediastinum formed by fusion of left and right brachiocephalic veins draining upper extremities. Due to its thin-walled structure and low pressure [=CVP (central venous pressure)], it is liable to external compression by tumor or enlarged nodes in mediastinum. Sometimes, this gets complicated by formation of thrombus in SVC lumen. Fortunately, azygos vein which also fuses with the SVC, offers collateral circulation in event of SVC obstruction. Hence, severity of SVC syndrome depends on rapidity of development of obstruction and the level of the obstruction with respect to azygos vein. Obstruction of the SVC above opening of the azygos vein allows drainage of venous return through collateral into azygos and ultimately into the SVC. This location of obstruction is better tolerated. Obstruction of the SVC below opening of the azygos vein is poorly tolerated since blood has to collateralize all the way to ICV.

Causes of SVC Syndrome

Small cell lung carcinoma (SCLC) is the most common cause of SVC syndrome. Non-small cell lung carcinomas (NSCLC) like adenocarcinoma or squamous carcinoma are also associated with SVC syndrome. Non-Hodgkin's lymphoma is other common cause. SVC syndrome is also seen in metastatic breast and colon cancers.

Up to 15% of patients with SVC syndrome have nonmalignant condition like mediastinal fibrosis or SVC thrombosis due to catheter or rarely due to pacemaker wire.

Clinical Features

Superior vena cava syndrome typically produces symptoms due to obstruction to venous drainage, concurrent compression of airway by tumor or airway edema, and underlying tumor. Typically, symptoms related to obstruction are worsened by bending forward or lying down.

Fullness and redness of face (suffusion) are the most common symptoms. Other symptoms commonly encountered are dyspnea, cough, dysphagia, headache and visual disturbance.

Investigations

Imaging

Chest radiograph reveals mediastinal widening. Computed tomography (CT) scan of chest with contrast is the investigation of choice. It provides location of tumor and further biopsy plan can be made. It also gives information about level of obstruction of SVC. CT should demonstrate absent or diminished contrast in SVC or innominate vein, and contrast opacification of collateral circulation.

Transesophageal echocardiography will distinctly identify luminal thrombus and differentiate it from extrinsic compression of the SVC.

Duplex ultrasound (Ultrasound + Color Doppler) is helpful to diagnose venous thrombosis due to central venous catheter in upper extremity.

Tissue Diagnosis

Antitumor therapy should not be started unless tissue biopsy is taken since biopsy becomes difficult when tumor starts shrinking after treatment. Inability of patient to lie down and hold breath requires intubation and ventilation for procedure of biopsy.

Treatment

Unless there is a dire emergency, oncological treatment should not be started till biopsy is done.

Treatment plan depends on underlying disease and urgency of symptoms. Venous access should be taken on lower extremities. Patient may need urgent airway access due to respiratory distress. Patients can have difficult mask ventilation and/or intubation due to airway and soft tissue edema. If difficult airway is anticipated, awake fiber-optic guided intubation should be planned. A rigid bronchoscope should be available to overcome any loss due to tracheal compression by the mass after sedation/anesthesia. Injection of long-acting muscle relaxant should be avoided. SCLC, lymphoma, and germ cell tumors respond very well to chemotherapy.

by mansdocs.com

Corticosteroids are added to chemotherapy regimen in lymphoma patients. In our experience, it takes at least 3–5 days for significant improvement to cause extubation even in patients with most chemosensitive tumors like lymphomas.

Radiotherapy is given for other tumors which are not chemosensitive, but are radiation sensitive.

Stents

Intravascular wire stents are used as adjunct in the palliative patients or absence of an underlying malignant disease. Stents offer faster relief of symptoms within 2 days in most of the patients. Since these stents are metallic, further magnetic resonance imaging (MRI) becomes impossible.

SPINAL CORD COMPRESSION

Three cancers commonly metastasizing to spine are breast, lung and prostate.

Underlining mechanism is mostly compression due to epidurally located tumor or due to pathologic fracture fragment. This is termed as metastatic epidural spinal cord compression (MESCC). Long-standing compression leads to neurological deterioration due to ischemia caused by arterial or venous occlusion, vasogenic edema, and demyelination.

Paravertebral neuroblastomas and lymphomas reach the spinal canal through an intervertebral foramen and directly compress the spinal cord.

Back pain is the most common presenting symptom. Neurological symptoms usually follow after 7 weeks of first episode of back pain. Motor dysfunction is second most common symptom. Plain radiographs of spine are done initially in patients with back pain as a screening test. Vertebral body fractures, lytic or sclerotic lesions, spinal deformity, paraspinal masses, reduced joint space in case of disk prolapse are usually picked up on plain radiographs. MRI of spine is the gold standard imaging modality for assessing spinal cord compression.

When a patient presents with a suspected malignancy and back pain, neurologic examination should be done to rule out myelopathy. If myelopathy is present, patient should be given high-dose dexamethasone and shifted for the MRI. If MRI is positive for spinal cord compression, steroids should be continued. A neurologist should be involved in the management of these patients.

Corticosteroids are elixir for acute neurologic deterioration with MESCC. Effects of corticosteroids can be characterized into:

- Analgesia effect-reduced tumor-associated inflammation
- Antiedema-improve short-term neurologic function by reducing spinal cord edema
- Chemotherapeutic effect-in lymphoma, multiple myeloma and breast cancer.

Patients should be given rest, proton pump blockers, or H2 receptor antagonist and glycemic control. Non-opioid analgesics, followed by opioids are prescribed consistent with World Health Organization (WHO) pain ladder. Specialist pain consultation should be done.

Emergency surgery or radiation plan for spinal decompression should be made on case to case basis.

Further treatment plan (radiation, surgery, chemotherapy) should be chalked out with discussion with oncologist.

BRAIN METASTASES AND INCREASED INTRACRANIAL PRESSURE

Tumors which commonly metastasize to brain are lung, breast cancer and melanoma.

Lung and melanoma usually have multiple brain metastasis, compared with solitary tumor in breast cancer. They are usually supratentorial, and at watershed areas or junction of gray and white matter.

Clinical features are similar to intracranial SOL like headache, neurologic deficits, seizures, and signs of increased intracranial pressure (ICP). Common locations of metastasis are usually borders of the territories of the major arteries (watershed areas) and at the gray-white matter junction.

Patients present to emergency department (ED) or ICU with altered mental status or convulsions. Increased ICP is common occurrence. A CT scan should be performed. This will reliably differentiate it from cerebral hemorrhage and hydrocephalus.

Since vasogenic edema is underlying mechanism, corticosteroids are first-line of treatment. Dexamethasone with dose of 16–24 mg/day or more is usually prescribed. Effects of mannitol and hyperventilation are temporary and sometimes used to bridge to some definitive therapy.

Surgical treatment is commonly offered in a young patient with breast cancer with solitary brain metastasis. For surgically unresectable tumors, whole-brain radiation

by mansdocs.com

therapy (WBRT) is offered. Survival is up to 6 months with WBRT and 1–2 months with only supportive care.

HYPERVISCOSITY SYNDROME

Blood is a nonhomogeneous fluid which is mixture of plasma (serum), red blood cells and leukocytes. Increased viscosity due to any of the component of the blood affects its flow. Imagine how swiftly water flows as compared to honey. Hyperviscosity leads to impairment in tissue perfusion.

Etiopathogenesis

- *Disorders of red cells*: Polycythemia
- *Disorders of plasma*: Dysproteinemia in multiple myeloma, and Waldenstrom macroglobulinemia (WM) (monoclonal gammopathy)
- *Disorders of white cells*: High white cell count in leukemias.

Viscosity of blood is determined by molecular weight and concentration of its contents. Shape of molecule and charge it bears, also determine viscosity.

Due to abundance of hemoglobin, hematocrit is the most important determinant of blood viscosity. Serum proteins also contribute, but to lesser extent due to lesser concentration.

Hyperviscosity syndrome (HVS) due to immunoglobulins (Igs): IgM has largest molecular weight and likely contributes most. Other mechanisms which play role are molecule shape and electric charges.

Rouleaux are formed due to cationic immunoglobulins reducing repellant forces between anionic red blood cells. This leads to decreased tissue perfusion due to impaired flow of RBC through microvasculature.

Normal serum viscosity (SV) is 1.2-2.8 (cP).

Generally, it is observed that patients are asymptomatic at SV less than 3. However, there is poor correlation between SV and symptoms. On the one hand, there are reports of retinal changes at SV of 2.1[WNL (within normal limits)]. On the other hand, many patients with WM are asymptomatic at SV greater than 4.

Diagnosis

There are no specific clinical features of HVS. Symptoms are usually due to impaired tissue perfusion. Neurologically, symptoms like headache, altered mental status, vertigo, ataxia, or paresthesias are commonly seen. Mucosal bleeding occurs due to proteins coating platelets and preventing aggregation. Bleeding is commonly seen from gums, nose (epistaxis) and gastrointestinal (GI) tract.

The classic triad of HVS is described as neurologic abnormalities, visual changes and bleeding. However, not all features are seen commonly in clinical practice.

Impaired tissue perfusion in HVS may cause congestive heart failure, acute tubular necrosis, and lead to multiorgan failure and death, if untreated.

Fundoscopic examination is mandatory in patients with suspected HVS. Vascular changes start at peripheral retina and spread to center as disease progresses. Initial finding is dilated, engorged sausage-like retinal veins known as fundus paraproteinaemicus.

As HVS progresses, it causes complete retinal vein occlusion, and flame-shaped hemorrhages. Visual disturbances may progress to blindness if not treated.

Pseudohyponatremia due to hyperproteinemia is commonly seen. Hypercalcemia is also seen. Serum protein ratio may be reversed in HVS due to immunoglobulins. Red cell rouleaux are seen on peripheral smear.

Treatment

Plasmapheresis is the treatment of HVS. It achieves rapid results in IgM-related HVS.

However, IgA- or IgG-related HVS requires many sessions. A session typically involves 1–1.5 times the blood volume exchange.

In setup where plasmapheresis is not available, phlebotomy with removal of 500 mL of blood can reduce severity of HVS. With phlebotomy, intravascular volume should be replaced with normal saline. Packed red cells should be given if Hb is less than 7 g%.

Loop diuretics are used to treat hypercalcemia and SV. Intravascular dehydration or hypovolemia should be avoided as it may worsen tissue perfusion.

In general, blood transfusion should be avoided till SV is reduced as hematocrit contributes a lot to blood viscosity.

Definitive treatment to control the underlying disease should be started as early as possible.

Hyperleukocytosis and Leukostasis

Hyperleukocytosis is defined as white blood cell (WBC) count more than 100,000/mL. It is commonly seen in acute lymphoblastic leukemia (ALL) with 11q23 rearrangement, and acute monocytic leukemia (AML) subtypes M3, M4 and M5.

by mansdocs.com

Hyperleukocytosis usually indicates poor prognosis.

Pulmonary leukostasis causes dyspnea and cough. Severe cases may have pulmonary hemorrhage. Other signs and symptoms are similar to HVS.

There might be pseudohypoxia in arterial blood gas report due to leukocytes rapidly consuming plasma oxygen.

Intracranial hemorrhage can occur due to cerebral leukostasis. Leukapheresis is generally started at blast count more than 100,000/mL or the presence of symptoms related to hyperviscosity or leukostasis. In ALL, leukapheresis is avoided till WBC more than 200,000/mL.

With hyperleukocytosis, leukpheresis is done till symptoms have resolved or WBC count is reduced to less than 50,000/mL.

Patients with hyperleukocytosis are at risk for TLS and should receive prophylaxis for it.

MALIGNANT PERICARDIAL EFFUSION

It may be due to primary tumor like mesothelioma or more commonly due to local or distant metastasis in case of breast and lung cancers or in lymphomas. Either ways, it carries poor prognosis with median survival of less than 1 year.

Signs and Symptoms

They depend on rapidity with which the fluid accumulates. Even a small fluid accumulation can cause tamponade if it accumulates fast. On the other hand, pericardium can accommodate large volume up to a liter or more without clinical instability if it accumulates slowly.

Presenting complains are dyspnea, fatigue, and chest discomfort. Muffled heart sounds, narrow pulse pressure, and pulsus paradoxus are usually present.

The classic Beck triad of distended neck veins, silent precordium, and hypotension in cardiac tamponade is rarely seen in malignancy as more often the fluid accumulation tends to be subacute rather than acute.

Diagnosis

Electrocardiograph rules out other causes of chest discomfort like angina. ECG may show low-voltage complexes with nonspecific repolarization (ST-T) changes. Electrical alternans is not a sensitive sign for pericardial effusion or cardiac tamponade.

Bedside, echocardiography is diagnostic for both effusions. It helps in guided pericardiocentesis.

Treatment

Asymptomatic effusions should not be drained for therapeutic purpose even if they are large. If patient has hypotension or other signs of clinical instability or findings of tamponade on echo, pericardiocentesis should be done under echocardiographic guidance. Biochemistry of fluid reveals exudative nature of effusions with high protein, and LDH levels. Acidic nature of pericardial fluid (pH < 7.3) indicates high disease burden and poor prognosis. Cytology should be done to confirm presence of malignant cells in pericardial fluid. Remember, cytology is not a sensitive test.

Pigtail catheter is usually left in situ till definitive therapy, since fluid may reaccumulate.

Once patient is stabilized, further treatment should be planned. Systemic chemotherapy is given for chemosensitive tumors. For others, treatment options are either pericardial injections of chemotherapy agents like bleomycin, carboplatin, and mitomycin C or surgical procedures like percutaneous balloon pericardiotomy, or video-assisted thoracoscopic (VATS) pericardial window.

AIRWAY OBSTRUCTION

Any primary or metastatic tumor arising from anywhere between the base of the tongue and the terminal bronchioles can give rise to airway obstruction. Primary bronchogenic carcinoma is the most common cause. Tumors of thyroid, esophageal, or mediastinal tumors can cause external compression of airway causing obstruction.

Signs and Symptoms

Dyspnea is usual presenting symptom. Hemoptysis and cough are present depending on location of tumor. Symptoms usually progress over a period of time in slow growing tumors. Occasionally, patients get exacerbation of symptoms due to retained secretions, infections or bleeding.

Presentation may be confused with chronic obstructive pulmonary disease (COPD), asthma, or bronchitis. Severe cases present with respiratory distress and stridor.

There is stridor, or wheeze on auscultation. Severe cases have silent chest. Obvious abnormalities like thyroid swelling, cervical lymphadenopathy or features of SVC syndrome are sometimes seen.

Diagnosis

Chest radiographs can be done for initial screening but it will not give much information.

by mansdocs.com

CT scan is more diagnostic and gives insight into level of obstruction and helps to plan treatment.

Flexible bronchoscopy is used for diagnosis in elective cases. In borderline cases, it may worsen partial obstruction into complete one. Rigid bronchoscopy can be used for diagnostic and therapeutic purposes.

In elective settings, flow-volume loop on spirometry can demonstrate pattern of airway obstruction. In patients on ventilator, flow-volume loop or flow/time graph gives similar information.

Treatment

Relief of obstruction is priority. Patients may need emergency intubation and ventilation. Upper airway obstruction may need an urgent tracheostomy and sometimes an emergency cricothyroidotomy, while waiting for this procedure for emergency airway management. Rigid bronchoscopy allows intervention like removal of tumor causing obstruction, control of bleeding, placement of stent. It also gives access for tissue diagnosis.

Silicone, metallic or hybrid stents are used to relieve obstruction. Stents give immediate relief of symptoms. However, evidence is lacking for change in long-term survival outcome.

Radiation Therapy

For radiosensitive tumors, external beam therapy is used for new cases and local brachytherapy is used for previously radiated cases.

Lymphomas, SCLCs, and germ cell tumors respond very well to systemic chemotherapy.

by mansdocs.com

CHAPTER

62

Post-cardiac Arrest Syndrome

Yash Javeri

INTRODUCTION

Post-cardiac arrest syndrome is a complex pathophysiological state that results after return of spontaneous circulation (ROSC) following a successful cardiopulmonary resuscitation. It is a unique and complex combination of pathophysiological processes including post-cardiac brain injury, post-cardiac myocardial dysfunction and systemic ischemia/reperfusion response. This state is often complicated by the unresolved primary pathological process that leads to cardiac arrest. This term has aptly replaced the previous terminology of post-resuscitation syndrome as post-resuscitation denotes the end of the act of resuscitation, whereas to achieve optimal survival with good neurological function, a much more complex and intensive phase of management has to begin after ROSC. In the second half of the 20th century, there is significant improvement in achieving ROSC from cardiac arrest, but long term and meaningful survival after ROSC has still not improved significantly. Translation of improved ROSC rates into better long-term survival rates requires a well-planned multidisciplinary approach for comprehensive post-cardiac arrest care. Simple restoration of blood pressure and oxygenation does not necessarily improve survival. Careful assessment and maintenance of regional organ and tissue perfusion is vital in improving final outcome. It is pivotal to avoid secondary brain injury in various phases of post-cardiac arrest period. Post-cardiac arrest care has got much required attention in last decade. Integrated post-cardiac arrest care is a vital link of American Heart Association's chain of survival. The aim is to reduce early mortality because of hemodynamic perturbations and delayed morbidity and mortality from multiorgan failure and brain injury (Fig. 1).

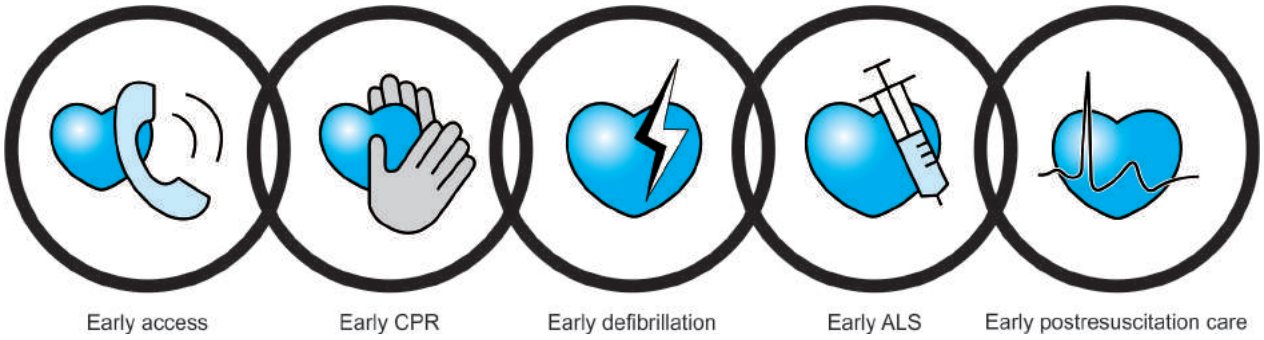


Fig. 1: American Heart Association's chain of survival.
(ALS: Advance life support; CPR: Cardiopulmonary resuscitation).

by mansdocs.com

PATHOPHYSIOLOGY

During cardiac arrest, complete whole body ischemia of variable duration leads to a complex cascade of pathophysiological processes which produces post-cardiac arrest brain injury, myocardial dysfunction and systemic ischemia/reperfusion response. The unresolved pathological process that caused the arrest and underlying comorbidities further complicates the situation. Although prolonged whole-body ischemia initially causes global tissue and organ injury, additional damage occurs during and after reperfusion.

Post-cardiac Arrest Brain Injury

Post-cardiac arrest brain injury contributes largely to morbidity and mortality. Brain has limited tolerance to ischemia, which predisposes it to early hypoxic injury. Mechanisms of brain injury are complex and include excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascade and activation of cell death signaling pathways. Hypoxemia/hypercarbia induced loss of cerebral autoregulation produces a unique response to reperfusion. Immediately after ROSC, there is a brief period of cerebral hyperemia, which theoretically should help perfusion, but it actually exacerbates brain edema and leads to reperfusion injury. Hyperoxia at this stage further exacerbates free radical induced neuronal injury. It is followed by a prolonged period of impaired reflow (the "no-reflow phenomenon"). This is because of microvascular dysfunction and intravascular thrombosis even in the presence of normal cerebral perfusion pressure. Hypotension, hypoxia, cerebral edema, seizures, hyperglycemia and hyperthermia can perpetuate secondary brain injury at this stage, and hence should be aggressively managed. Hyperglycemia is common in post-cardiac arrest patient and is associated with poor neurological outcome. Post-cardiac arrest brain injury can manifest as brain death, coma, seizures, myoclonus and neurocognitive dysfunction, which ranges from memory deficits to persistent vegetative state.

Post-cardiac Arrest Myocardial Dysfunction

Post-cardiac arrest myocardial dysfunction manifests as transient global myocardial dysfunction, which is responsive to therapy and reversible in 24–48 hours with judicious hemodynamic optimization and optimal organ support. Myocardial stunning leads to arrhythmias, reduced cardiac output with variable heart rate and blood pressure. There is no irreversible injury or infarction as coronary blood flow is preserved.

Transient increase in heart rate and blood pressure after ROSC can be due to increase in local and systemic increase in circulatory catecholamines. This global dysfunction is transient and full recovery usually occurs. Cardiac index reaches the nadir about 8 hours after resuscitation, improving further in next 24 hours and usually return to normal by 72 hours.

Systemic Ischemia and Reperfusion Response

Cardiac arrest is physiologically like the most severe form of shock state, in which delivery of oxygen and metabolic substrate is reduced and removal of waste product of metabolism is also reduced. During cardiopulmonary resuscitation, a compensatory increase in systemic oxygen extraction occurs, leading to decreased central venous oxygen saturation ($ScvO_2$). As early as 3 hours after ROSC, microcirculatory dysfunction along with myocardial dysfunction and hypoperfusion leads to release of various cytokines, soluble receptors, free radical and endotoxins in the blood stream, which indicates activation of endothelial system, immunological and coagulation pathways. This phenomenon is known as systemic ischemia/reperfusion response; reperfusion syndrome and manifests as a state of impaired oxygen delivery and utilization, impaired vasoregulation, multiple organ failure, and increased susceptibility to infection. This condition mimics sepsis. The major reason behind the microcirculatory reperfusion disorders is activation of blood coagulation without adequate activation of endogenous fibrinolysis.

PERSISTENT PRECIPITATING PATHOLOGY

Cardiac arrest can be because of many pathological conditions like acute coronary syndrome, pulmonary embolism, hemorrhage, sepsis, and many toxidromes. These conditions may complicate the course of post-cardiac arrest syndrome. These conditions should be identified and treated aggressively. Due precautions are needed to avoid reoccurrence.

PHASES OF RESUSCITATION SYNDROME

Standardization of time frame is required to provide protocol-based care, correct prognostication, and to perform epidemiological and interventional studies. A time-based approach divides post-arrest period into phases. Initial 20 minutes after ROSC constitute immediate post-cardiac

by mansdocs.com

arrest phase. Starting 20 minutes after ROSC till up to 6–12 hours is the early post-cardiac arrest phase when timely interventions to limit ongoing injury and organ support therapies are most effective. Most post-resuscitation deaths occur in this stage. From 6–12 hours till up to 72 hours is the intermediate period during which cardiac and systemic functions improve but microcirculatory dysfunction ensues. Splanchnic and renal microcirculatory dysfunction predisposes to multiple organ dysfunction syndromes. A phase of recovery begins after 72 hours. A more reliable prognostication and better predictability of outcome can be done in this phase (Fig. 2).

THERAPEUTIC STRATEGIES

A multidisciplinary, comprehensive, time sensitive care tailored to available resources is the key to reversing the pathophysiological changes of post-cardiac arrest syndrome (Flowchart 1).

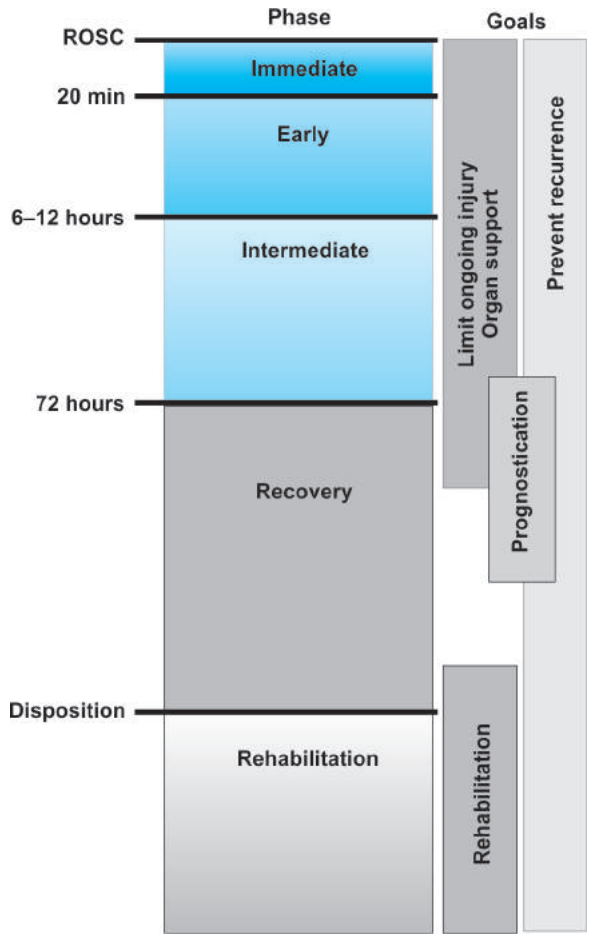


Fig. 2: Phases of post-cardiac arrest syndrome (ROSC: Return of spontaneous circulation).

MONITORING

Monitoring can be divided into three categories as mentioned in the Table 1.

ORGAN-SPECIFIC EVALUATION AND SUPPORT

Cardiovascular System: Early Hemodynamic Optimization

Early goal directed therapy (EGDT) is an approach to restore the balance between systemic oxygen delivery and demands (Table 2).

Mainstay of therapy is intravenous fluids, inotropes, vasopressors and blood transfusion. The optimal mean arterial pressure (MAP) in post-cardiac arrest state has not been defined. Slightly higher MAP is desirable after taking into consideration the patient's baseline blood pressure, severity of myocardial dysfunction and coronary ischemia. The purpose is to offset the effect of the no reflow phenomenon in brain and maintenance of the cerebral perfusion. Intra-aortic balloon pump augments both cerebral and coronary perfusion in this setting. The value of more invasive cardiac support like percutaneous cardiopulmonary bypass, transthoracic ventricular assist devices and extracorporeal membrane oxygenation is yet not established.

Antiarrhythmic Drugs

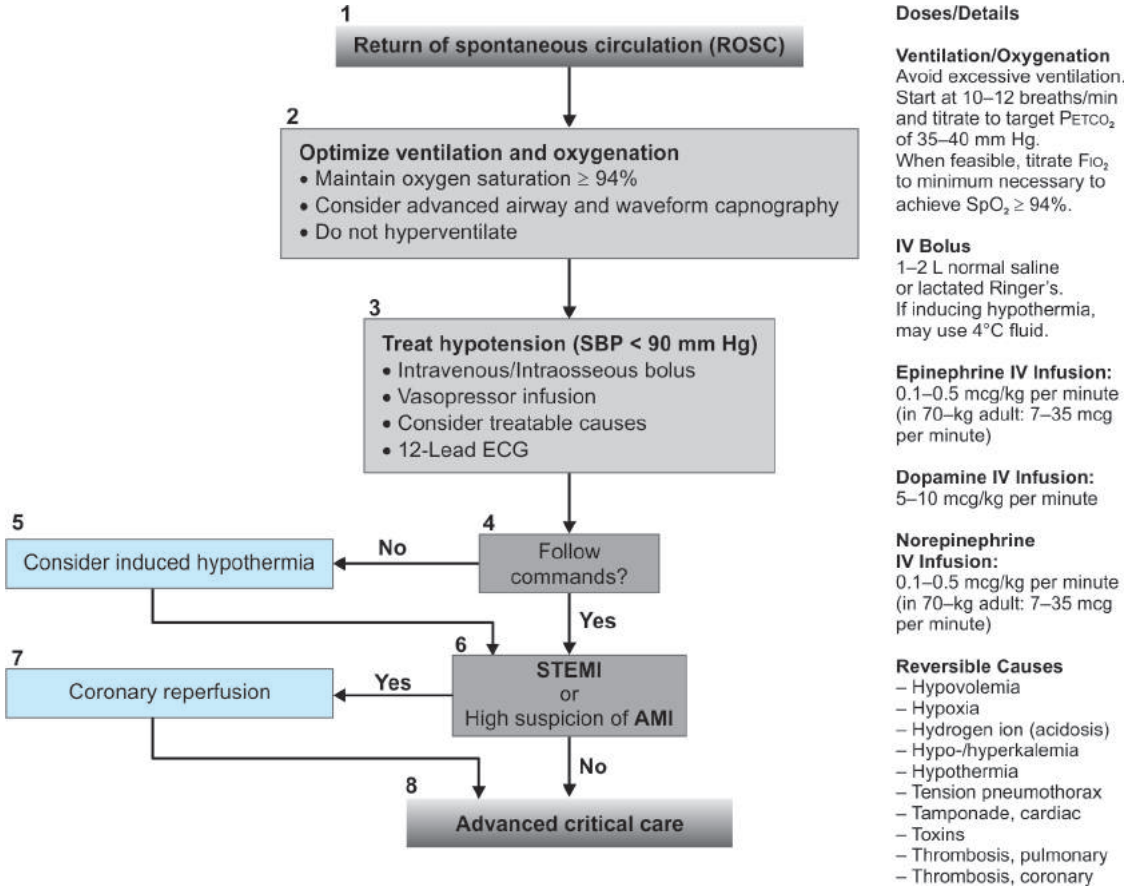
Prophylactic use of antiarrhythmics is not recommended, but if any agent was required during advanced cardiac life support (ACLS), then it need to be continued as maintenance therapy. If arrhythmia was the cause of cardiac arrest then pacemaker or implantable cardioverter-defibrillator should be considered. If arrhythmia was secondary to myocardial ischemia then early reperfusion is desired. Electrolytes should be monitored serially and corrected. Given the cardioprotective effects of β-blockers, they may be used judiciously.

NEUROPROTECTIVE STRATEGIES

All measures should be directed to optimize cerebral perfusion pressure, which can be accomplished by either reducing the elevated intracranial pressure (ICP) and/or maintaining a normal to slightly elevated MAP. Head end of bed should be kept elevated to aid venous drainage. Flexion of neck should be prevented to avoid compression

by mansdocs.com

Flowchart 1: Immediate post-cardiac arrest care



(SpO_2: Oxygen saturation; ECG: electrocardiogram; AMI: Acute myocardial infarction; F_{IO_2}: Fractional inspired oxygen; P_{ETCO_2}: Pressure end-tidal CO_2; SBP: Systolic blood pressure; STEMI: ST segment elevation myocardial infarction).

of neck veins. Avoid tracheal suctioning as coughing leads to increase in ICP. All other maneuvers which are known to increase ICP should be avoided and if warranted should be done with appropriate care.

Hypermetabolism after cardiac arrest can cause fever, which perpetuates neuronal injury by increasing cerebral metabolic rate. Temperature should be closely monitored after resuscitation and fever should be treated aggressively. Seizures should be promptly treated to avoid secondary brain injury. All agents are equally effective. Thiopentone has not been found to afford neuroprotection. Continuous electroencephalography (EEG) monitoring is desirable. There is no role of prophylactic anticonvulsants. Myoclonus can be troublesome and is best treated with clonazepam. Hyperglycemia is common in post-cardiac arrest syndrome and also during induced hypothermia, and it must be treated with insulin targeting moderate glucose control. Numerous agents have been studied till date, but none has been recommended for routine use.

THERAPEUTIC HYPOTHERMIA

The cerebral metabolic rate decreases approximately 7% for every 1°C fall in core body temperature. Thus, hypothermia minimizes the mismatch between oxygen supply and demand, hence imparting neuroprotection. Mild therapeutic hypothermia is evidently the only therapy known to improve neurological outcome after ROSC. It is strongly recommended in postventricular fibrillation out-of-hospital cardiac arrest. It may also be beneficial for other rhythms or in-hospital cardiac arrest. Patient should be cooled to 32–34°C as soon as possible after ROSC for at least 12–24 hours. Mild hypothermia develops spontaneously after cardiac arrest. The concept of permissive hypothermia states that post-cardiac arrest patients, who

by mansdocs.com

develop a mild degree of hypothermia spontaneously, should not be actively rewarmed.

Therapeutic hypothermia can be divided into induction, maintenance and rewarming phase (Fig. 4).

Hypothermia can be induced either by internal cooling techniques like intravenous cold fluids, lavage of body cavities and endovascular cooling catheter. External cooling techniques like ice packs placed or cooling blankets can also be used. Table fans deployed along with sponging is often sufficient to induce hypothermia. This technique is quite common and effective in most of Indian hospitals. There are smart temperature management systems available in India. There are benefits and drawbacks of each modality and the available resources should be utilized in a judicious manner (Fig. 5).

Shivering is common during induction phase, and it must be abolished by using sedatives with or without neuromuscular blockade. Magnesium sulfate administered during induction phase of hypothermia has been found to be beneficial by reducing shivering, increasing rate of cooling, producing antiarrhythmic effects and also has independent neuroprotective effect. Hypothermia may also produce detrimental effects, which can adversely affect the outcome. It can lead to increased blood viscosity, impaired coagulation, reduced cardiac output, arrhythmias, increased susceptibility to infection, diuresis

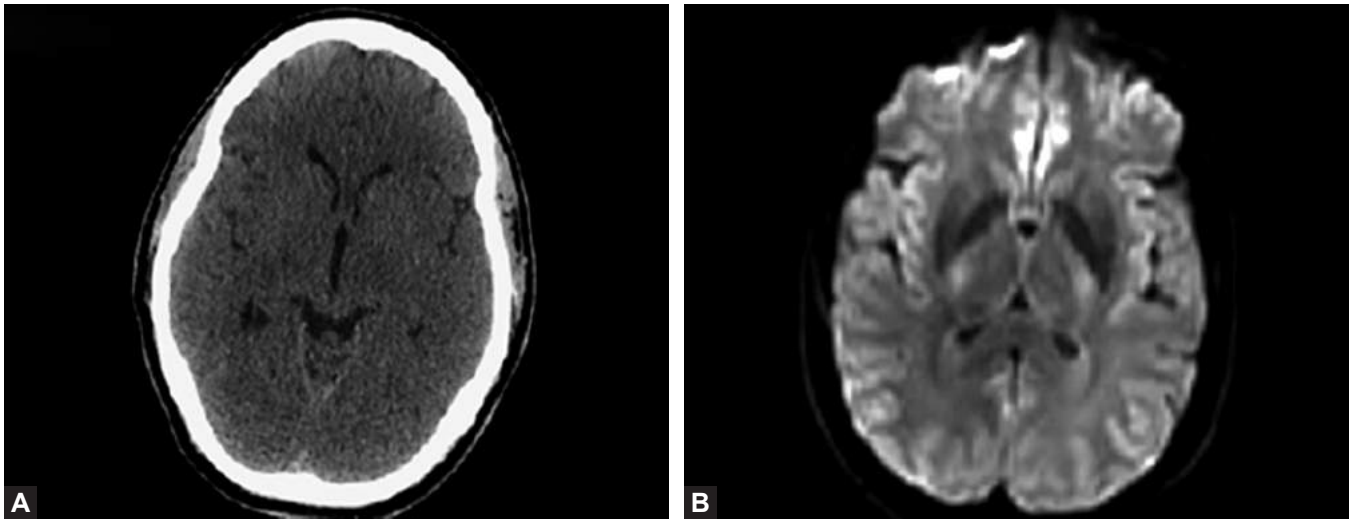
Table 1: Monitoring in post-cardiac arrest syndrome.

Intensive care monitoring
• ECG
• Temperature (bladder, esophagus)
• Oxygen saturation using pulse oximetry
• Invasive blood pressure, central venous pressure and $ScvO_2$
• Arterial blood gases and lactate
• Urine output
• Routine hematology and biochemistry
Advanced hemodynamic monitoring
• Echocardiography
• Cardiac output monitoring
• Judicious use of pulmonary artery catheter
Neurological monitoring
• EEG on indication or continuously for early seizure detection
• CT/MRI (Figs. 3A and B)
• MR spectroscopy, PET scan
• Xenon enhanced CT scan of brain for cerebral blood flow

(EEG: Electroencephalography; $ScvO_2$: Central venous oxygen saturation; PET: Positron emission tomography).

Table 2: Hemodynamic goals.

• Central venous pressure	8–12 mm Hg
• Mean arterial pressure	65–90 mm Hg
• Central venous oxygen saturation	>70%
• Hematocrit	>30%
• Lactate	<2 mmol/L
• Urine output	>0.5 mL/kg/hr
• Oxygen delivery index	>600 mL/min/m^2



Figs. 3A and B: Imaging characteristics of anoxic injury. (A) Computed tomography demonstrating diffuse cerebral edema, sulcal effacement and loss of gray-white differentiation. (B) Diffusion weighted imaging MRI showing hyperintensity in the gray matter mainly in the frontal lobes.

by mansdocs.com

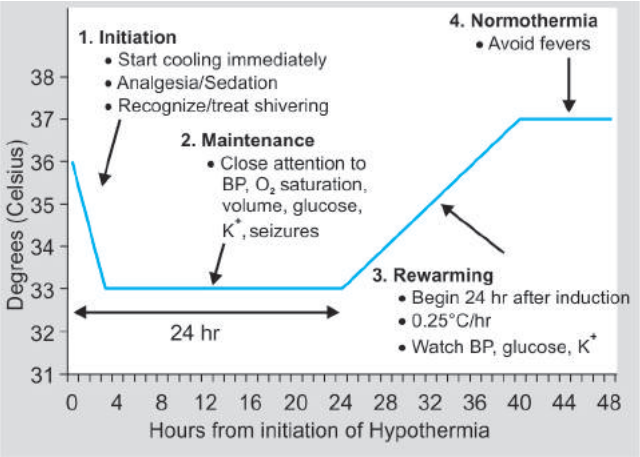


Fig. 4: Phases of therapeutic hypothermia.

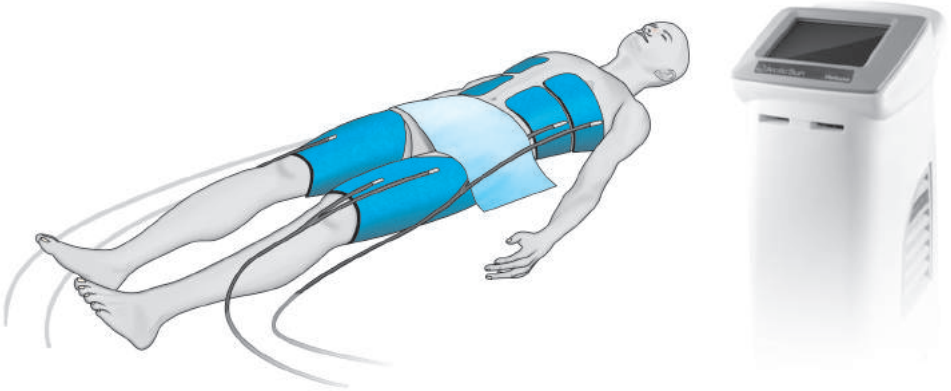


Fig. 5: Integrated temperature management system.

induced dyselectrolytemia and hyperglycemia. Clearance of several drugs from body is affected. Continuous temperature monitoring should be done to avoid fluctuations in temperature. Rewarming should be done slowly at a rate of 0.25–0.5°C per hour. Due care should be taken during the cooling and rewarming phase because metabolic rate, electrolyte levels and hemodynamic parameters may change rapidly.

Respiratory System

Respiratory dysfunction varies from inadequate spontaneous efforts to complete absence of respiratory efforts requiring full ventilatory support. Level of ventilatory support should be titrated according to blood gas, respiratory rate and work of breathing. Hyperoxia even for an hour after ROSC has been found to harm postischemic neurons therefore fractional inspired oxygen (FiO_2) should be targeting SpO_2 of 94–96%.

Hypocapnia induced cerebral vasoconstriction decreases cerebral blood flow and precipitates cerebral ischemia which worsens ischemic injury. Hyperventilation also reduces cerebral blood flow by increasing cerebral venous and ICPs. Hyperventilation also decreases cardiac output as a result of increased airway pressures and auto PEEP. Hence, routine hyperventilation is not recommended. Ventilation to normocarbic levels is appropriate. Once hypothermia has been instituted, tidal volumes should be reduced as metabolic rate is slowed and CO_2 production decreases. End-tidal CO_2 monitoring should be instituted. Hypoventilation leading to hypoxia or hypercarbia could also increase ICP and compound acidosis.

Renal System

Routine catheterization of bladder should be done to closely monitor urinary output. Low-dose dopamine does not accord any beneficial or protective effect on splanchnic

by mansdocs.com

or renal blood flow, and hence not recommended in acute oliguric renal failure. Nephrotoxic agents should be avoided and drugs eliminated via kidneys should be used with caution with appropriate dose modification. Renal failure is associated with higher mortality.

Gastrointestinal System

The splanchnic circulation is assuming increased importance for targeted therapy in improving long-term outcome and survival. Tonometric analysis of systemic: gastric mucosal pCO_2 gradient and its correction to achieve splanchnic resuscitation may be important strategy in resuscitation protocols in near future. Routine stress ulcer prophylaxis is strongly recommended. Starting enteral feeding early has been found to preserve intestinal mucosal integrity, and also reduces incidence of bacterial translocation from gut.

Adrenal Insufficiency

Relative adrenal insufficiency may develop following physiological stress of cardiac arrest. However, routine use of steroids in post-arrest period is unproven and not routinely recommended.

Persistent Precipitating Pathology

Early diagnosis and appropriate management of pathology that led to arrest is imperative. If left uncorrected, cardiac arrest can reoccur which further complicates the pathophysiological process. The review of Hs and Ts mnemonic of ACLS to find etiology of cardiac arrest is must. Where acute coronary syndrome is suspected to be the cause of arrest, troponin T levels at 12 hours after ROSC, have been reported to be 96% sensitive and 80% specific, whereas creatinine kinase-MB levels have been found to be 96% sensitive and 73% specific for the diagnosis of acute myocardial infarction. In the initial 12 hours after ROSC, there specificity is low because of false positive elevation due to myocardial contusion during compression. Those patients who have electrocardiographic criteria for ST elevation myocardial infarction should undergo immediate coronary angiography followed by percutaneous cardiac intervention if indicated. Pulmonary embolism should be properly investigated, and treated aggressively.

Sepsis

A phenomenon called endotoxin tolerance along with therapeutic hypothermia produces a state of immunosuppression leading to increased risk of infections and sepsis in post-cardiac arrest state. Surveillance cultures should be send in this phase. Pneumonia is particularly common. Sepsis should be managed with EGDT as per surviving sepsis campaign guidelines.

Consequences of Cardiopulmonary Resuscitation

The incidence of complications of cardiopulmonary resuscitation like rib or sternum fracture, hemopneumothorax, pericardial tamponade, pulmonary contusion and abdominal trauma are widely considered to be low. Misplacement of endotracheal tubes and other devices should be actively looked for. Chest X-ray should be done routinely. Artificial respiration using noninvasive ventilation methods can often result in gastric insufflation. Pancreatitis, while often transient, may develop in post-cardiac arrest state and requires high index of suspicion.

Sedation and Neuromuscular Blockade

There is insufficient data to recommend routine sedation during first 24 hours after ROSC. Sedation may be required for prevention of shivering during induction phase of hypothermia. Sedation may also be for patient-ventilator dyssynchrony. Both opioid analgesics and sedative hypnotics like benzodiazepines or propofol may be used. If neuromuscular blockade is required to control shivering even after deep sedation, intermittent boluses are preferred over continuous infusion.

PROGNOSTIC FACTORS

Unfortunately, absence of any stand alone or multimodal predictor model of outcome makes prognostication a difficult task. Detailed neurological examination done serially and still remains one of the most widely validated and reliable predictor of functional outcome after cardiac arrest. Any four findings from the following clinical signs at 24 hours have been found to predict poor neurological outcome.

- Absent corneal reflex at 24 hours.
- Absent pupillary response at 24 hours.
- Absent withdrawal response to pain at 24 hours.
- No motor response at 24 hours.
- No motor response at 72 hours.

Glasgow Coma Scale motor score of less than or equal to two is associated with poor outcome.

Absence of pupillary light response, corneal light reflex, or motor response to painful stimuli on third day remains a reliable predictor of poor neurological outcome.

by mansdocs.com

When neurological examination is done, confounding factors like hypotension, shock, electrolytes abnormalities, sedation, muscle relaxant, endocrinopathies and temperature disorders should be eliminated. Combining clinical examination with other adjunctive tests enhances the accuracy and precision of prognostication.

ADJUNCTIVE INVESTIGATIONS

Neurophysiological Tests

Absence of bilateral N20 component of somatosensory evoked potential with median nerve stimulation has been found to be better than the bedside neurological examination as a predictor of poor neurological outcome. Specific EEG patterns are known to depict poor functional outcome. However, EEG should not be used as a stand-alone modality for prognostication.

Imaging

Well-defined prospective studies are required to fully understand the utility of neuroimaging modalities including cerebral blood flow by xenon CT, positron emission tomography, and MR spectroscopy.

Biochemical Markers

Blood neuron-specific enolase (NSE) and S100β levels and cerebrospinal fluid creatine phosphokinase-BB levels have showed promising results to prognosticate functional outcome after cardiac arrest, but require further studies for validation. NSE more than 33 μg/L is associated with poor outcome.

ETHICS

Treating physician should be able to prognosticate using objective scores. End of life care issues should be addressed timely. Ethical dilemmas need to be addressed intelligently involving all the stake holders. Institutional policies need to be reviewed with considerations on local legislations. Involvement of ethics team and clergy are often beneficial. Communication needs to be clear, consistent, comprehensive and well documented. The transplant team should be involved at the time of treatment withdrawal and retrieve organs after cardiac arrest has occurred.

SUMMARY

The objective of care in post-cardiac arrest patients is to improve survival with good neurological outcome. The pathophysiology of post-cardiac arrest syndrome is complex. Early hemodynamic optimization and therapeutic hypothermia have definite evidence. Secondary neurological insults should be avoided. Prognostication should include clinical and adjunctive tools.

BIBLIOGRAPHY

1. Adrie C, Laurent I, Monchi M, et al. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care. 2004;10(3):208-12.
2. Booth CM, Boone RH, Tomlinson G, et al. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA. 2004;291(7):870-9.
3. Mongardon N, Dumas F, Ricome S, et al. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care. 2011;1(11):45.
4. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. Resuscitation. 2003;57(3):231-5.
5. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122 (18 Suppl 3): S768-86.
6. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation. 2008;118(23):2452-83.
7. Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67(2):203-10.

by mansdocs.com

CHAPTER

63

Intra-abdominal Hypertension and Abdominal Compartment Syndrome

Rajesh Pande, Puneet Khanna

A 25-year female with type II diabetes mellitus and acute pancreatitis presents with septic shock. She is hemoconcentrated with severe metabolic and lactic acidosis. Her treatment includes fluids, vasopressors and antibiotics. Patient receives about 10 L of intravenous (IV) fluid resuscitation in the first 20 hours after hospital admission. After 24 hours of therapy, she develops worsening hypotension, oliguria, hypoxemia, hypercarbia. The peak inspiratory pressure on the ventilator increases from 20 cm to 40 cm. The intra-abdominal pressure (IAP) was 26 mm Hg and a decompressive laparotomy resulted in immediate resolution of renal, pulmonary and hemodynamic compromise.

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) occur in many intensive care unit (ICU) settings and not limited to trauma settings only. The bladder pressure measurements are valuable in assessing whether IAH is contributing to organ dysfunction. Spot check is not a good choice as "Spot" intra-abdominal pressure (IAP) checks often delay the diagnosis. Continuous IAP monitoring allows early detection and early intervention for IAH before ACS develops. There is significant lack of awareness among the intensivists about ACS, IAP monitoring and its management.

Table 1: Interpretation of intra-abdominal pressure.

IAP (mm Hg)	*Interpretation*
• 0–5	Normal
• 5–10	Common in most ICU patients
• >12	Intra-abdominal hypertension
• 15–20	Dangerous IAH-noninvasive interventions may be considered
• 20–25	Impending ACS-strongly consider decompressive laparotomy

(IAP: Intra-abdominal pressure; ICU: Intensive care unit; IAH: Intra-abdominal hypertension; ACS: Abdominal compartment syndrome).

INTRA-ABDOMINAL HYPERTENSION AND ABDOMINAL COMPARTMENT SYNDROME

Abdominal compartment syndrome as defined by World Society of the Abdominal Compartment Syndrome (WSACS) is a sustained IAP more than or equal to 20 mm Hg [with or without an abdominal perfusion pressure (APP) ≥60 mm Hg] that is associated with new organ dysfunction or failure (Tables 1 and 2). Another classification based on the timing of IAH divides it into four categories (Table 3).

The diagnosis can be divided into three components: identifying patients at risk, recognizing the clinical signs associated with transition of IAH to ACS and proactively carrying out diagnostic measures to confirm the suspected diagnosis. A rising IAP may affect the organ functions adversely (Fig. 1).

Table 2: World Society of the Abdominal Compartment Syndrome (WSACS) grading of IAH.

Grade	*WSACS definition (mm Hg)*
I	12–15
II	16–20
III	21–25
IV	>25

(IAH: Intra-abdominal hypertension).

by mansdocs.com

Table 3: Timing designations of abdominal compartment syndrome.

Type	Description	Example
• Chronic	• Seen in progressive abdominal disease process	• Cirrhosis with massive ascites
• Acute	• Associated with disease or injury in the abdomen requiring intervention	• Intestinal ischemia, abdominal trauma
• Subacute	• Associated with extra-abdominal disease process	• Aggressive fluid resuscitation for sepsis regardless of the focus
• Hyperacute	• Development of ACS intraoperatively during repair of extra-abdominal injuries with massive resuscitation	• Massive resuscitation for shock during operative intervention for chest trauma, major vascular trauma, packing of abdominal injury

(ACS: Abdominal compartment syndrome).

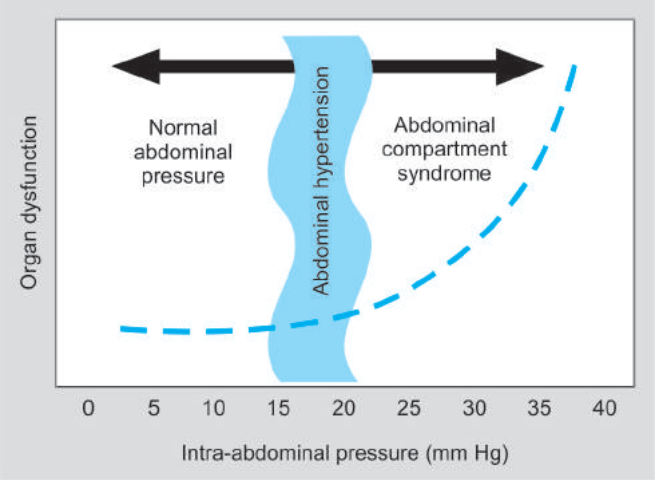


Fig. 1: Relationship between intra-abdominal pressure and organ dysfunction.

Etiology and Risk Factors

- Diminished abdominal wall compliance
- Acute respiratory failure with elevated intrathoracic pressure
- Abdominal surgery with primary fascial or tight closure
- Major trauma or burns
- Prone positioning, head of bed more than 30°
- High body mass index (BMI), central obesity
- Increased intraluminal contents
- Gastroparesis
- Ileus
- Colonic pseudo-obstruction
- Increased abdominal contents
- Hemoperitoneum/pneumoperitoneum
- Ascites/liver dysfunction
- Capillary leak/fluid resuscitation
- Acidosis (pH < 7.2)
- Hypotension
- Hypothermia (Core temperature < 33°C)
- Multiple transfusion (> 10 units of blood/24 hr)
- Coagulopathy [platelets < 55,000/mm^3 or prothrombin time (PT) > 15 seconds, or partial thromboplastin time (PTT) > 2 times normal or international normalized ratio (INR) > 1.4]
- Pancreatitis
- Oliguria
- Sepsis
- Damage control laparotomy.

Pathophysiology of Intra-abdominal Hypertension

The physiological insult due to raised IAP (compounded by aggressive fluid resuscitation in hypovolemic conditions) causes ischemia and inflammation leading to tissue edema including bowel wall and mesentery causing intra-abdominal hypertension.

IAH Physiological Sequelae of Rise in Intra-Abdominal Pressure (Fig. 2)

Cardiac

Increased IAP causes compression of the vena cava with decreased venous return and elevated intrathoracic pressures with negative cardiac effects. The result is decreased cardiac output leading to increased systemic vascular resistance (SVR), increased cardiac workload, decreased tissue perfusion and SvO_2 (mixed venous oxygen saturation), high lactates. The elevations in pulmonary arterial wedge pressure (PAWP) and central venous pressure (CVP) could be misleading. Eventually, if untreated, the cardiac insufficiency may cause cardiac arrest.

Pulmonary

Increased IAP causes elevation of the diaphragms with reduction in lung volumes. There is release of cytokines and immune hyperresponsiveness resulting in increased intrathoracic pressure (which further reduces venous return to heart, exacerbating cardiac problems), increased peak pressures, reduced tidal volumes, barotrauma,

by mansdocs.com

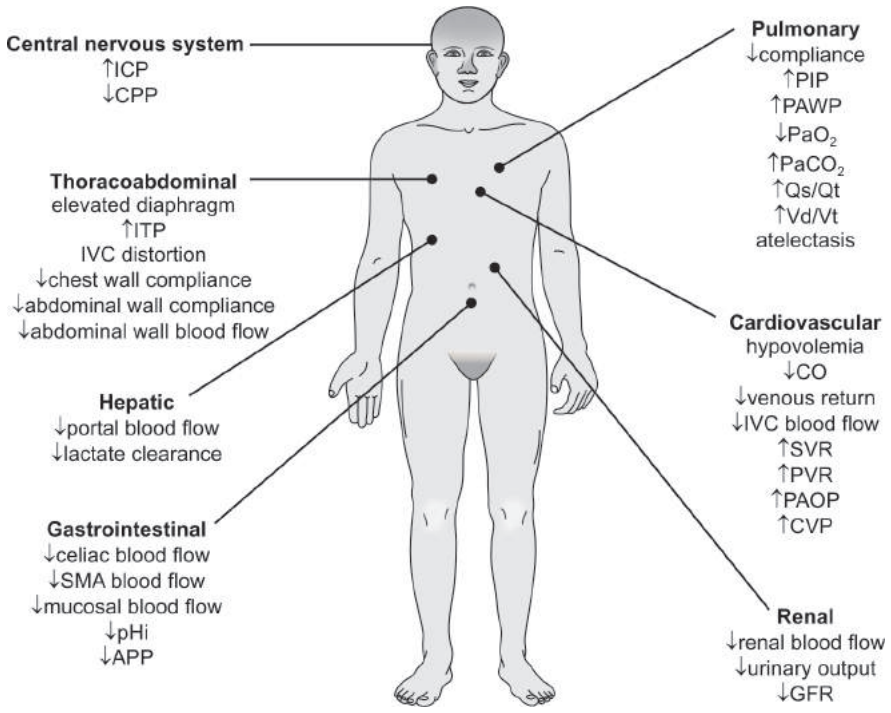


Fig. 2: Pathophysiological implications of intra-abdominal hypertension.

(ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; PIP: Peak inspiratory pressure; PAWP: Pulmonary arterial wedge pressure; Qs/Qt: Shunt fraction; Vd/Vt: Ratio of dead space to tidal volume; GFR: Glomerular filtration rate; SVR: Systemic vascular resistance; PVR: Pulmonary vascular resistance; PAOP: Pulmonary artery occlusion pressure, CVP: Central venous pressure).

atelectasis, hypoxia, hypercarbia and development of extra-pulmonary acuter respiratory distress syndrome (ARDS).

Gastrointestinal

Increased IAP causes compression/congestion of mesenteric veins and capillaries with reduced cardiac output to the gut, resulting in decreased gut perfusion, increased gut edema and leak, ischemia, necrosis, cytokine release, neutrophil priming. It also results in bacterial translocation, development and perpetuation of systemic inflammatory response syndrome (SIRS) and further increases in IAP.

Renal

Elevated IAP causes compression of renal veins and arteries, reducing cardiac output to kidneys resulting in decreased renal artery and vein flow, renal congestion and edema, decreased glomerular filtration rate (GFR), acute tubular necrosis (ATN), renal failure, oliguria/anuria.

Neuro

The increased intrathoracic pressure causes an increase in elevated IAP which causes increase in superior vena cava (SVC) pressure with reduction in drainage of SVC into the thorax, resulting in increased CVP and internal jugular vein (IJV) pressure, increased ICP, decreased cerebral perfusion pressure (CPP), cerebral edema, brain anoxia and brain injury. The direct impact of IAP causes immediate increases in intracranial pressure (ICP), internal jugular pressure (IJP) and CVP [also in PAOP (pulmonary artery occlusion pressure)].

Miscellaneous

Elevated IAP reduces perfusion of surgical and traumatic wounds. It reduces blood flow to liver, bone marrow, etc. and causes pooling of blood in pelvis and lower extremity, causing poor wound healing and dehiscence, coagulopathy, immunosuppression, deep venous thrombosis (DVT) and pulmonary embolus (PE) risks.

Prevalence in Critically Ill

A multicenter prospective epidemiological study conducted in 13 ICUs across six countries revealed the prevalence of IAP more than 20 mm Hg plus organ failure as 10.5% in medical ICU (MICU) and 5% in surgical ICU

by mansdocs.com

(SICU), whereas the prevalence of IAP more than 20 mm Hg was quite high as 29.8% in MICU and 27.5% in SICU. Another prospective cohort study found 43% hospital mortality in patients with IAH (defined as IAP ≥ 12 mm Hg). The patients with IAH were significantly more acutely ill, admitted with more organ failures, underwent mechanical ventilation more often, showed delayed weaning, and had significantly higher hospital mortality rates and longer ICU stays. Out of 12% who had ACS, only 20% survived.

Abdominal compartment syndrome is associated with poor patient outcome as documented by a study done in liver transplant patients, where an IAP value of 23 mm Hg was associated with delayed weaning, 24 mm Hg with renal dysfunction and 25 mm death with death.

The clinical signs of IAH are unreliable and only show up late in clinical course (once ACS occurs). IAH and ACS increase morbidity, mortality and ICU length of stay.

Preventive therapy plus early detection and intervention can reduce these complications in many patients. Monitoring early (not waiting for clinical signs) in all high-risk patients allows early detection and early intervention.

Measurement of Intra-abdominal Pressure

Intra-abdominal pressure monitoring: The urinary bladder pressure monitoring through the Foley's catheter is the current standard for monitoring abdominal pressures and is comparable to direct intraperitoneal pressure measurements, but is noninvasive (Figs. 3 and 4). In fact, this is more reliable and reproducible than clinical judgment.

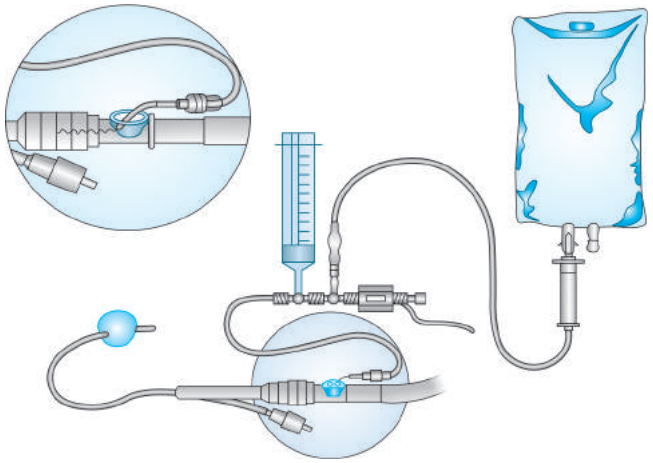


Fig. 3: Urinary bladder pressure monitoring system.
(50 mL of sterile saline is instilled into the bladder via the aspiration port of the Foley catheter with the drainage tube clamped. An 18-gauge needle attached to a pressure transducer is then inserted in the aspiration port, and the pressure is measured. The transducer should be zeroed at the level of the pubic symphysis).

Abdominal Perfusion Pressure

APP = MAP - IAP

The APP reflects actual gut perfusion better than IAP alone.

Optimizing APP to more than 60 mm Hg should be the primary endpoint. In fact, optimizing APP tomore than 60 mm Hg reduces incidence of ACS and death. Delay in abdominal decompression may lead to intestinal ischemia; therefore, decompression should be done early.

MANAGEMENT OF INTRA-ABDOMINAL HYPERTENSION/ABDOMINAL COMPARTMENT SYNDROME

- Fluid resuscitation is a two-edged sword. Fluids improve cardiac indices if the patient has inadequate RV filling. However, over-resuscitation leads to worsened edema.
- Abdominal perfusion pressure—optimizes fluids first then add vasopressors. Target an APP more than 60 mm Hg.
- Sedation and paralytics may be helpful.
- Colloids may be used.
- Hemofiltration.

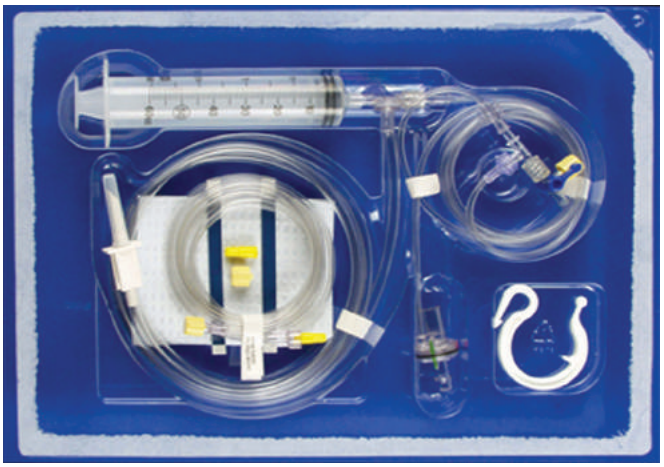
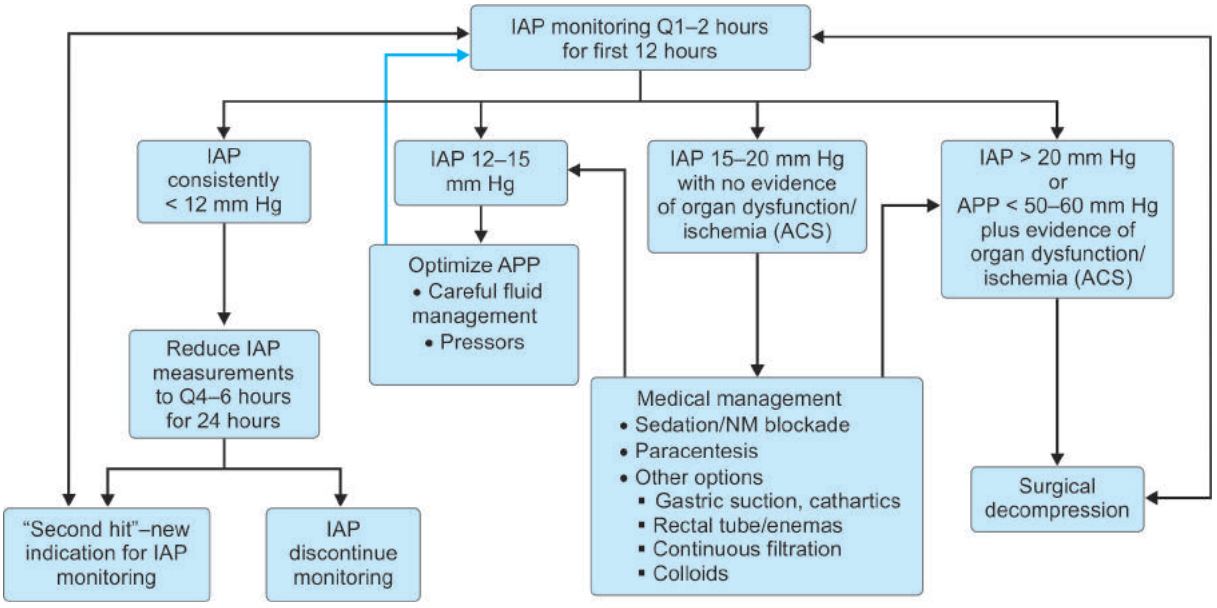


Fig. 4: Commercially available urinary bladder pressure monitoring systems.

by mansdocs.com

Flowchart 1: University of Utah: Intra-abdominal pressure monitoring protocol



(IAP: Intra-abdominal pressure; ACS: Abdominal compartment syndrome; APP: Abdominal perfusion pressure; NM: Neuromuscular).

- Paracentesis.
- Need significant free fluid on USG.
- Decompressive laparotomy.

One should not wait for signs of ACS to be present, before the decision to check IAP is taken. Monitor all high-risk patients early and often IAP should be monitored like a vital sign. If there is development of critical pressure, intervene immediately without delay before severe organ dysfunction sets in. USG- or CT-guided percutaneous drainage should be attempted initially to relieve IAP, if possible. IAP monitoring algorithm of University of Utah is shown in Flowchart 1.t

by mansdocs.com

CHAPTER

64

Nutrition in a Critically Ill Patients

Pravin Amin

INTRODUCTION

Malnutrition is very common in acutely ill patients, occurring in nearly 50% of hospitalized patients. This number may be higher in critically ill patients, and may be even more in third world population. Hospital malnutrition has been associated with an increased risk of complications, particularly in surgical patients. A malnourished patient is more likely to have infectious morbidity, a prolonged hospital stay, and increased mortality. Malnutrition in hospitalized patients also increases hospital costs. The critically ill intensive care unit (ICU) patient's nutritional status often becomes significantly deteriorates during their ICU stay. Over 50% of all ICU patients worldwide are significantly underfed based on the calories and protein they are prescribed in the early part of their ICU stay.

Methods to improve or maintain nutritional intake are known as nutrition support. These include:

- Oral nutrition support (e.g. fortified food, additional snacks and/or sip feeds)
- Enteral tube feeding (e.g. the delivery feed directly into the gut via a tube)
- Parenteral nutrition (PN) (e.g. the delivery of nutrition intravenously).

These methods can improve outcomes, but which of these is more effective and safe can indeed be multifaceted.

NUTRITIONAL ASSESSMENT IN THE CRITICALLY ILL

The central goal of nutritional support is to meet the energy requirements of metabolic methods, to support the hypermetabolism associated with critical illness, and to diminish protein catabolism. Indirect calorimetry is considered the gold standard to determine patient's caloric needs. Controversy remains when comparing indirect calorimetry with weight-based equations such as the Harris-Benedict Equation (HBE). Although there is new evidence to support that the HBE may closely estimate caloric needs when multiplied by certain stress factors, there is also contradictory evidence demonstrating that the HBE can lead to either over- or underfeeding, which is associated with a multitude of complications.

Exogenous protein is required for wound healing and to counter protein catabolism. Generally about 1.0–1.5 g/kg/day of protein is required, depending on the degree of illness and injury. A severely injured patient may require in excess of 2.0 g/kg/day to replace the large quantities of protein lost due to catabolism.

There are numerous ways to estimate protein requirements. One simple method is to look at the ratio of non-protein calories to grams of nitrogen. A typical ICU patient requires a ratio of 150 carbohydrate calories to 1 gram of nitrogen to prevent the use of protein as an energy source.

Nitrogen balance = [protein intake (in grams)/6.25] – [24-hour urine urea nitrogen (UUN) (in grams) + 4].

GENERAL STRATEGY FOR ICU PATIENTS

- Whenever nutritional support is indicated, the enteral route is the first choice and should be initiated within 24 hours.

by mansdocs.com

- At least 60% of the energy target should be reached within 3 days after admission in the ICU; if not, consider prescribing supplemental PN.
- *Practical indications*:
  - Pre-existing malnutrition
  - Fasting or insufficient oral intake for more than 3–4 days in a patient unable to eat
  - Severe trauma and burns
  - Critically ill patients (prolonged mechanical ventilation, significant multiorgan system disease)
  - Extensive small bowel resection.
- *Contraindications*:
  - Three conditions are incompatible with enteral nutrition (EN): severe shock state, nonfunctional gut (i.e. anatomic disruption, obstruction, ischemia) and severe peritonitis.
- *Energy target*:
  - *Acute and initial phases of critical illness*: 20–25 kcal/kg body weight/day (energy excess to be avoided)
  - *Postacute phase and long-term stay*: 25–30 total kcal/kg body weight/day
- *Timing*:
  - Enteral nutrition should be started within 24 hours.

Enteral Nutrition

Enteral nutrition maintains gut integrity and immune function. EN has demonstrated functional benefits including the support of gut-associated lymphoid tissue (GALT) and mucosa-associated lymphoid tissue (MALT) that is critical for maintaining the gut-associated immune function.

Evidence to support the effectiveness of enteral tube feeding has grown significantly, and randomized controlled trials have shown that the initiation of enteral tube feeding can result in a reduction in hospital stays and medical complications.

All guidelines recommend early EN using a nasogastric tube in preference to PN in patients with no major gut dysfunction, and the use of promotility drugs if EN is not tolerated.

Protocols should be in place to optimize the enteral delivery of nutrients, promote intestinal tolerance and to stimulate gut contractility. Appropriate placement of enteral access is desirable.

Enteral nutrition may not be possible in patients with intestinal obstruction, ischemia, acute peritonitis, or bowel in discontinuity. Relative but not absolute contraindications include severe malabsorption, shock or sepsis, or multiple high-output fistulas.

Enteral nutrition support refers to the provision of calories, protein, electrolytes, vitamins, minerals and fluids via an enteral route. For all critically ill patients receiving EN, semirecumbent position is recommended. Most critically ill patients receiving EN, gastric feeding rather than post-pyloric feeding is recommended. Gastric feeding can be delivered via an orogastric tube, a nasogastric tube, or a percutaneous gastric tube. Post-pyloric feeding should be used if gastric feeding is not tolerated or contraindicated. In practice, it is generally considered acceptable that enteral feeding be initiated in critically ill patients at a rate of 10–20 mL/hr (standard formulation) for 6 days and then incrementally increased to the target rate. There is increasing consensus that the routine checking of gastric residual volumes is unnecessary in asymptomatic patients receiving tube feedings.

Parenteral Nutrition

Parenteral nutrition support refers to the provision of calories, amino acids, electrolytes, vitamins, minerals, trace elements and fluids via a parenteral route. PN is generally indicated for patients who do not tolerate or have contraindications or both to EN. Until recently, early total parenteral nutrition (TPN) was not seen as a potential advantage in terms of clinical outcome because the frequent metabolic and infectious complications observed during the early postinjury phase were classically related to TPN.

The provision of early PN (up to 48 hours) to patients with absolute or relative contraindications to EN does not alter mortality. Additionally, there is no consistent evidence in critically ill patients suggesting that early PN improves the number of ventilator-free days or length of stay in the ICU or hospital. In balance, evidence suggests that early PN in well-nourished critically ill patients, whether given as the sole therapy or supplemental to EN, does not reduce mortality and may be associated with an increased risk of nosocomial infections. The optimal time for starting PN in critically ill patients is unknown.

Parenteral nutrition must be delivered via a central venous catheter because its high osmotic load is not well tolerated by peripheral veins.

Short-term PN is generally delivered through a subclavian, internal jugular, or femoral central venous catheter. The femoral site is least desirable because there may be an increased risk of catheter-related infections.

Long-term PN requires a tunneled central venous catheter (e.g Hickman catheter, Groshong catheter, or implanted infusion port) or a peripherally inserted central catheter.

by mansdocs.com

Single lumen central venous catheters should be dedicated solely for the infusion of PN, while multiple lumen central venous catheters should have one port dedicated solely for the infusion of PN.

These interventions may decrease the infectious complications associated with PN.

Dextrose: Dextrose-containing stock solutions are available in a variety of concentrations, most commonly 50–70%.

Amino acids and electrolytes: Amino acid solutions contain most essential and nonessential amino acids. The caloric contribution of amino acids is approximately 4 kcal/g. Electrolytes are contained in the buffer of the amino acid solution, usually in small quantities. The amino acid stock solutions come in concentrations ranging from 5.5% to 15%. Higher concentrations are useful for minimizing volume and electrolytes delivered to patients.

Lipids: Lipids are provided as an emulsion that may be infused separately or added to the mixture (three-in-one mixture). Lipid emulsion consists of long-chain omega-6 triglycerides derived from soybean and safflower oils and then emulsified using egg phospholipids and glycerin. The caloric contribution of a typical lipid emulsion is 2 kcal/mL in 20% emulsion and 1.1 kcal/mL in 10% emulsion. Other types of lipids (e.g. refined olive, soybean, and fish oil emulsions) are now available.

Vitamins and trace elements: Numerous clinical trials have examined the effect of antioxidants on critically ill patients when given as single nutrients (e.g. selenium) or as a combination of nutrients (selenium, copper, zinc, vitamin A, vitamin C, vitamin E, and N-acetylcysteine). Meta-analyses show improvement in the duration of mechanical ventilation, but no differences in infectious complications, hospital length of stay, or ICU length of stay.

Monitoring: Routine monitoring of PN includes measurement of fluid intake and output, as well as selected laboratory studies. It is reasonable to measure serum electrolytes, glucose, calcium, magnesium, and phosphate daily until they are stable. It is similarly reasonable to measure aminotransferases, bilirubin and triglyceride at least once each week during treatment.

Complications: Patients who receive PN support are at risk for infection, adverse metabolic effects, and complications related to venous access. Bloodstream infection—patients receiving PN are at increased risk of acquiring a bloodstream infection, compared to patients who have central venous catheters but are not receiving PN. Metabolic effects—PN is associated with metabolic complications, including hyperglycemia, serum electrolyte alterations, macro- or micro-nutrient excess or deficiency, refeeding syndrome, Wernicke's encephalopathy, and hepatic dysfunction.

Peripheral parenteral nutrition (PPN) is a type of PN that can be delivered through a peripheral intravenous catheter because it has an osmolarity lower than that of conventional PN. To deliver adequate nutrients, either a large volume or a high fat formulation must be infused. Frequent replacement of intravenous access is often necessary. Despite an osmolarity lower than conventional PN, PPN is still quite hyperosmolar and irritating to the peripheral veins.

Immunonutrition

The basic aims of immunonutrition are to modulate the immune response with naturally occurring nutrients so as to curb tissue injury, reduce infection rates and morbidity, and so eventually improve survival. Immunonutrition refers to therapy in which a particular nutrient is administered to induce a specific metabolic function not usually associated with nutrition support. These "immune-enhancing diets" are thought to modulate the immune system, facilitate wound healing, and reduce oxidative stress.

L-Arginine

The amino acid L-arginine becomes an essential nutrient under stress conditions because the normal quantities endogenously produced to maintain muscle mass are insufficient because of increased protein turnover after injury. Arginine is required for stimulation and release of growth hormone, prolactin, insulin and glucagon; plays a fundamental role in polyamine and nucleic acid synthesis. It is also a critical substrate for nitric oxide (NO) production, NO is an important mediator of vascular dilation, protein synthesis in hepatocytes, and electron transport in hepatocyte mitochondria. Evidence concerning the effects of arginine administration on mortality is lacking. In critically ill patients with sepsis, arginine supplementation led to excessive mortality compared with an isonitrogenous control diet. In patients undergoing major cancer surgery, arginine supplementation has been associated with reduced length of stay.

by mansdocs.com

Omega-3 Fatty Acids

Polyunsaturated fatty acids are a major component of cell membranes and consequently influence the structure and function of cellular membranes.

Fish oil contains high concentrations of eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid, which are naturally occurring omega-3 acids.

Glutamine supplementation was also associated with a lower rate of infectious complications and a shorter hospital stay. Suggesting that in critically ill patients, glutamine supplementation may be associated with a reduction in complication and mortality rates. As a single agent, glutamine supplementation has a broad spectrum of beneficial effects in humans. These include reducing infectious complications, acting as a trophic agent for the gastrointestinal tract, and upregulating the immune system. Clinical studies have demonstrated that parenteral and enteral glutamine supplementation is beneficial in patients after bone marrow transplantation, multiple trauma, critical illness, or surgery. In burn patients, improved immune cell function and a reduction in mortality with enteral glutamine have been demonstrated.

Selenium

Selenium is the most studied single nutrient. It is an important cofactor for the enzyme glutathione and exerts beneficial effects on immune function. Selenium deficiency has been associated with encephalopathy, progressive muscle weakness, myopathy and cardiomyopathy. In systemic inflammatory response syndrome (SIRS) patients, three separate selenium studies produced three different outcomes: one reported reduced mortality, one described a nonsignificant trend toward reduced mortality, and the final study reported no effect.

CONCLUSION

The primary goal of nutrition support therapy is to supply the substrate necessary to meet the metabolic needs of patients in whom adequate nourishment cannot be provided by mouth. These needs vary with the phase of critical illness. Optimizing nutritional therapy is based on fully understanding the premorbid nutritional status of the patient and the pathophysiology of the underlying critical illness. The enteral route is preferred in most circumstances, but there are specific situations in which TPN is necessary and may be beneficial.

BIBLIOGRAPHY

1. Cerra FB, Benitez MR, Blackburn GL, et al. Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. Chest. 1997;111(3): 769-78.
2. Heyland DK, Drover JW, Dhaliwal R, et al. Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. JPEN J Parenter Enteral Nutr. 2002;26(6 Suppl):S51-7.
3. Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA. 1998;280(23):2013-9.
4. McClave SA, Kozar R, Martindale RG, et al. Summary points and consensus recommendations from the North American Surgical Nutrition Summit. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):99S-105S.
5. Mueller C, Compher C, Ellen DM; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: Nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16-24.
6. Singer P, Berger MM, van den Berghe G, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr. 2009;28(4):387-400.

by mansdocs.com

CHAPTER

65

Approach to an Unknown Poisoning

Vikas Loomba, Ashish Bhalla

INTRODUCTION

Any substance if taken in any account, by any route, and produces harmful effects (the three D's—disease, deformity or death) over the body is called a poison.

A poison may have local, systemic or combined effects. The effects of the poison depend on the route of administration, dose and concentration of the poison, physical and chemical state of the poison, area of application, age of the patient, idiosyncrasy and tolerance.

It is important to remember that not all substances when ingested have a deleterious effect on the body. Substances, like adhesives, bathtub toys, blackboard chalk, candles, crayons, gums, ink, lipstick, water-based paint, shaving cream, soap, etc. are not dangerous when ingested.

Symptoms of poisoning may vary, but certain cardinal features may suggest a particular class of poisons (Table 1). Diagnosis is usually clinical but in some cases blood and urinary investigations may be of help. Treatment is usually supportive in most of the cases, and specific antidotes are necessary in less than 5% of the cases only.

Most of the poisonings are dose and concentration related. However, poisoning should be distinguished from hypersensitivity and idiosyncratic reactions, which are unpredictable and not dose related. Poisoning is recognized as an important health problem in many developed countries and is ill defined in many developing nations. Poisoning can be unintentional, suicidal and rarely homicidal. Data from poison information center of All India Institute of Medical Sciences (AIIMS) revealed the highest incidence of poisoning in the age range of 14–40 years with male preponderance and common mode of poisoning was oral (88%).

DIAGNOSIS

The diagnosis of the poisoning is dependent upon history, symptoms, signs and laboratory investigations. The constellation of various signs and symptoms that herald toxicity permits the recognition of a toxic syndrome or toxidrome.

History

A good history is the key to success in the management of poisoning. However, obtaining the history from a poisoned patient is difficult as the patient may be uncooperative, misleading or in altered sensorium. Family members, friends, prehospital personnel or previous medical records may provide vital information and aid in management.

Examination

Patient's stabilization take precedence over examination in emergency. Examination of a poisoned person needs to be focused with special attention toward vital signs, neurological status, pupils, skin, bowel and bladder, which permits the recognition of a toxidrome. Recognition of a toxidrome is of importance to manage patients with exposure to unidentified substances.

Identification of Toxidromes

In a patient with unknown overdose, a toxidrome can help in reaching a diagnosis and to anticipate other symptoms. Various common toxidromes include:

by mansdocs.com

Table 1: Symptoms caused by various poisons.

• Abdominal pain	• Caustics, cholinergic agents, cocaine, iron or salicylates
• Abdominal distension	• Caustics or anticholinergics
• Increased thirst	• Arsenic, atropine and lead
• Cough	• Acid or metal fumes, formalin, chlorine, copper or ammonia
• Odynophagia or dysphagia	• Corrosives, camphor, hydrogen sulfide or marine animal bites
• Toxic pancreatitis	• Copper, zinc, organophosphates or methanol
• Color of the vomitus	• Blue: codeine; green: copper sulfate or cannabis; brown: acid, alkali or zinc phosphide ingestion; hematemesis: manganese, alcohol, thallium or carbon tetrachloride
• Diarrhea	• Arsenic, boric acid, cyanide or iron
• Constipation	• Ergot alkaloids, calcium salts, lead, opium and arsenic
• Discoloration of urine	• Green urine: phenol or cresol; orange: rifampicin or phenothiazines; yellow: arsine; pink: aniline or mercury; purple: porphyria; blue: methylene blue; brown or black: naphthalene; red: phenolphthalein
• Oliguria	• Arsenic, phenol, carbon tetrachloride
• Polyuria	• Alcohol, mercury, nitrites, bismuth and digitalis
• Myalgias	• Copper, arsenic, lead or sea snake
• Rhabdomyolysis	• Bee stings, barbiturates, cocaine, heroin and snakebite
• Fever	• Arsenic, datura, barbiturates, cocaine, strychnine, salicylates, anticholinergics, antidepressants, curare and metal fumes
• Hypothermia	• Opiates, alcohol, carbon monoxide and barbiturates
• Rhinorrhea	• Iodine and arsenic
• Deafness	• Methyl alcohol, ergot, quinine, tobacco and aminoglycosides
• Vertigo	• Alcohol, cannabis, carbon monoxide, cyanide, ergot or tobacco
• Convulsions	• Cocaine, strychnine, opium, alcohol
• Tremors	• Alcohol, mercury, manganese, cocaine, arsenic

- *Cholinergic (organophosphates)*: Diarrhea, diaphoresis, urination, miosis, bradycardia, increased bronchial secretions emesis, lacrimation, salivation
- *Anticholinergic (antihistamines, tricyclic antidepressants)*: Hyperthermia, dry skin, dilated pupils, delirium, hallucinations, tachycardia, urinary urgency and retention
- *Sympathomimetics (cocaine, amphetamine)*: Diaphoresis, mydriasis, tachycardia, hypertension, hyperthermia and seizures
- *Narcotics (heroin, methadone)*: Miosis, hypoventilation, coma, bradycardia, hypotension
- *Withdrawal from alcohol, opioids, benzodiazepines, barbiturates*: Diarrhea, mydriasis, goose flesh, tachycardia, lacrimation, hypertension, yawning, cramps, hallucinations, seizures.

Lab Investigations

Investigations may be of some help in reaching to the diagnosis of unknown poisoning. Various investigations may include:

- *Complete blood cell count*:
  - *Anemia*: Chronic alcohol, arsenic, lead, opium.
  - *Polycythemia*: Arsenic, carbon monoxide, aniline, cobalt
  - *Leukopenia*: Aniline, arsenic, antimony, lead, chloramphenicol, sulfonamides
  - *Leukocytosis*: Snake bite, pilocarpine, thallium, titanium
  - *Thrombocytopenia*: Sulfonamides, promazine, chloramphenicol
  - *Pancytopenia*: Sulfonamides, erythromycin, chloramphenicol
  - *Bone marrow failure*: Beryllium, cadmium, fluoride, phosphorus, selenium
  - *Stippling*: Lead, antimony, bismuth, barbiturates
  - *Hemolysis*: Snake bite, arsine, copper sulfate, nitrofurantoin, lead
  - *Methemoglobinemia*: Aniline, nitrobenzene, nitrites, methylene blue, copper, toluidine.

by mansdocs.com

- *Urine*:
  - *Albuminuria*: Arsenic, mercury, phenol, thallium, chromate
  - *Hemoglobinuria*: Arsine, acetic acid, copper, nitrites, snake bite
  - *Hematuria*: Arsenic, allopurinol, mercury, phenols.
- *Blood sugar*
- *Electrolytes*: Presence of anion gap may help us in diagnosing poisoning due methanol, ethanol, paraldehyde, phenformin, iron, carbon monoxide, cyanide, hydrogen sulfide, isoniazid, ibuprofen, salicylates, sympathomimetics. Normal anion gap is between 6 and 14 mEq/L
- *Blood gas analysis*: To look for:
  - Acidosis or alkalosis
  - Defective oxygen extraction and utilization as in cyanide poisoning. Cyanide blocks process of oxidative phosphorylation.
- *Serum creatinine phosphokinase*: Helpful in patients with hyperthermia and increased muscle tone as in neuroleptic malignant syndrome or sympathomimetic toxidrome.
- *Electrocardiogram*: Frequent or continuous cardiac monitoring along with a 12 lead ECG is required to look for exposure to any potential cardio toxin like sympathomimetic agents, cyclic antidepressants, digitalis, beta-blockers, calcium channel blockers, arsenic, cyanide, carbon monoxide. We should look for changes in cardiac conduction, arrhythmia or ischemia. The triad of pseudo right bundle branch block consisting of R wave in aVR, S wave in lead 1 and S wave in aVL is highly sensitive indicator of sodium channel blockade from tricyclic antidepressant exposure. Ventricular bradyarrhythmia may occur with digitalis toxicity, and nonspecific ST-T changes in all leads may occur with lithium toxicity. Cocaine or carbon monoxide may produce ECG pattern of acute myocardial ischemia or infarction.
- *Drug screening*: Used for drugs of abuse like amphetamines, cannabinoids, cocaine, opioids. this is especially useful in diagnosis of unresponsive young adult patients presenting to emergency.
- *Imaging*: X-ray or CT abdomen may be helpful in case of radio dense materials like lead, heavy metals, enteric coated tablets or packets containing drugs. Hydrocarbons may cause "double bubble" sign in the stomach.
- *Endoscopy*: Useful in diagnosis and prognosis in caustic ingestion and should be done within 8–12 hours, no later than 24 hours.

MANAGEMENT

The priority is to stabilize the airway, breathing, circulation (ABCs) and to manage the life-threatening complications. Airway, breathing, circulation, disability, dextrose, definitive antidote and exposure comprise the "A, B, C, D, E" of management (Flowchart 1).

Clear the airway by repositioning the patient and institute suctioning if needed. Some may have respiratory depression and need respiratory assistance with a bag valve mask or ventilator. The toxic patient may unexpectedly lose airway control. So, aggressive airway management is of paramount importance. Patient's oxygenation status can be monitored with pulse oximetry but caution is needed in cases due to carboxyhemoglobin or methemoglobin, where in it may be normal.

Intravenous access should be established as soon as possible with two large bore IV cannula. The patient should be closely monitored because continued absorption of the ingested poison may lead to further deterioration. Frequent monitoring for alertness, oxygenation status and vital signs is needed. Toxins can produce hypotension by vasodilatation, myocardial depression or fluid losses from vomiting or diarrhea. In such patients, volume replacement with normal saline or Ringer's lactate is needed. If the blood pressure does not improve with fluid therapy, then vasopressors may be added. Desperate measures like intra-aortic balloon pump may be needed in resistant cases. Myocardial depression is common with calcium channel blockers and beta-blockers.

Tricyclic antidepressants and cocaine may cause arrhythmias like wide complex tachycardia and these are managed with sodium bicarbonate and lidocaine. Bicarbonate is given to achieve pH of 7.50–7.55.

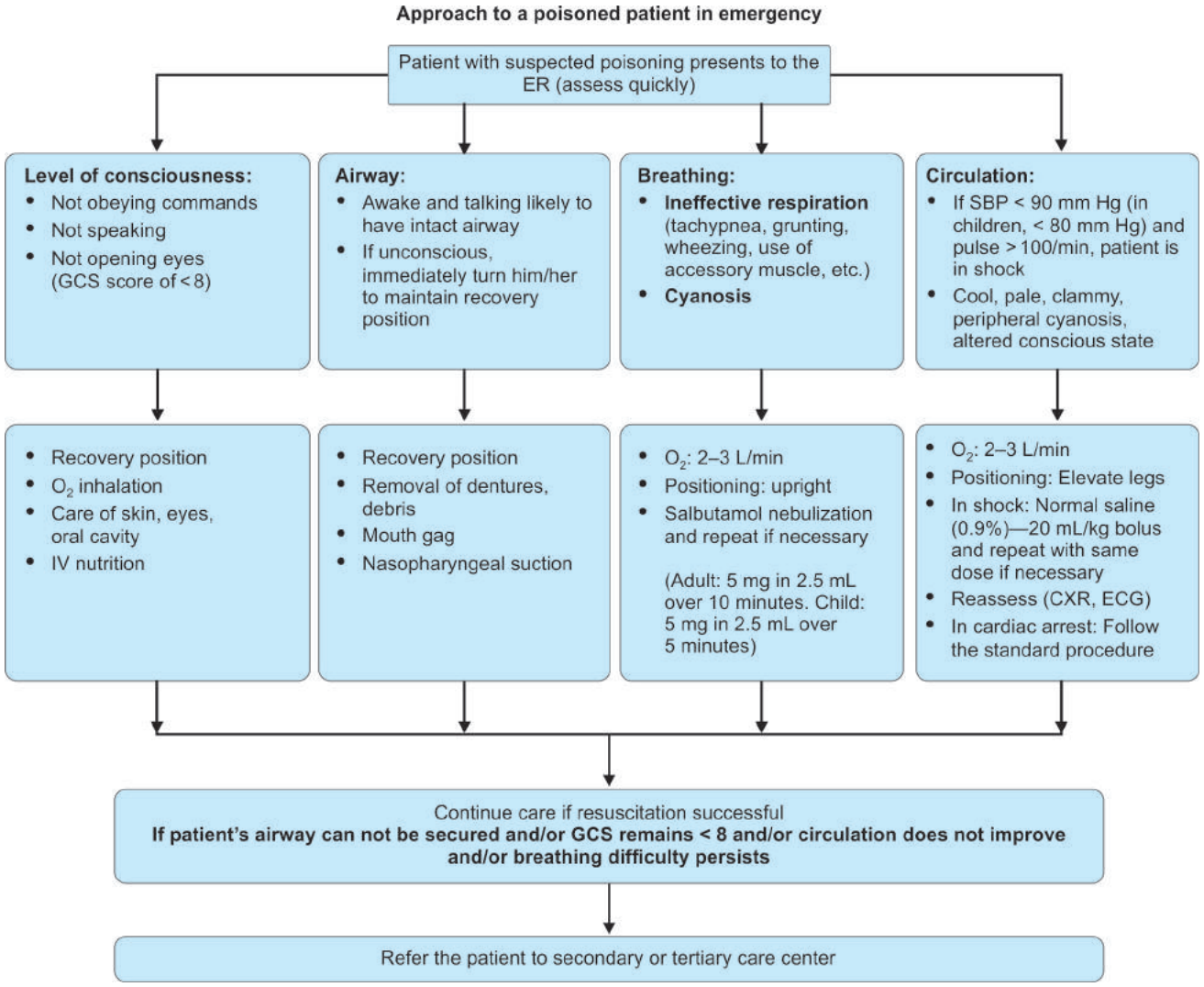
COMA COCKTAIL

The role of "coma cocktail" is controversial; however, it tends to cover most common poisonings, especially in areas where alcoholism and recreational drug abuse is a major problem.

Every patient of unknown poisoning should be given 50% dextrose unless the finger stick shows euglycemia or hyperglycemia. Naloxone, an opioid antagonist, has both diagnostic and therapeutic value. Give 0.4–2.0 mg IV will revert the symptoms of opioid toxidrome. Some opioids like pentazocine, diphenoxylate, propoxyphene, codeine may require up to 10 mg of naloxone to cause arousal.

by mansdocs.com

Flowchart 1: Initial assessment and management of a poisoning patient in emergency room (ER) (failure to resuscitate indicates referral to higher center).



(ER: Emergency room; GCS: Glasgow coma scale; SBP: Systolic blood pressure; ECG: Electrocardiogram; CXR: Chest X-ray; IV: Intravenous).

The dose is titrated until patient has stable respiration, i.e. respiratory rate more than 10 and pulse oximetry more than 92%. Thiamine should be given to all alcoholic patients whenever they present to emergency, preferably before dextrose.

Flumazenil, a benzodiazepine antagonist, can reverse benzodiazepine overdose. However, it should be used with caution in case of mixed drug overdoses as it can induce seizures in patients having co-ingestion of benzodiazepines with antidepressants or sympathomimetics. So flumazenil should be used judiciously in a patient of isolated benzodiazepine overdosage with persistent hypoxia or progressive respiratory depression.

REMOVAL OF POISON

The ultimate aim of management is reversal of the toxidrome. The effort is to:

- *Get rid of the poison from the system*:
  - *Decontamination*: Washing of skin and mucous membranes, gastric lavage, cathartics.
- *Control the symptoms*:
  - Symptomatic treatment
  - Specific antidote.

Decontamination

It is performed to limit the ongoing absorption of the toxin. We need to decontaminate the skin with water,

by mansdocs.com

eyes with isotonic solution and gut with a large bore (36–40 Fr) nasogastric tube. Decontamination of the gut is carried out in a critically ill patient with large toxic ingestion. In patients with depressed mental status and instability presenting to emergency, securing the airway and stabilization of vitals take priority. Gastric lavage is done by placing the patient in left lateral or head down position with ryles tube passed intranasally. Small all quotes (250 mL) of fluid is used each time till the returns are clear. It is contraindicated in case of ingestion of corrosive substance or hydrocarbon as there is a risk of aspiration, esophageal perforation, epistaxis, hypothermia and death. The role of emesis, activated charcoal and cathartics in decontaminating the gut is controversial. Ipecac-induced emesis is no longer recommended as it can lead to aspiration. Activated charcoal is used in the dose of 1 g/kg to the maximum of 100 g for prescription drug overdose. It is not useful in pesticides, hydrocarbons, alcohol, acids, alkalies, iron, lithium, solvents poisoning. Adverse effects are aspiration pneumonitis, bowel obstruction and perforation.

Whole bowel irrigation with warmed polyethylene glycol electrolyte solution at 0.5–1.0 L/h may be useful in limiting further absorption of the toxin. It is continued till the rectal effluent is clear which usually takes 4–6 hours. This is done for large and potentially fatal ingestion of substances that are not bound by charcoal like iron, lithium, lead or sustained release preparations. It is contraindicated in bowel obstruction, perforation, gastrointestinal (GI) hemorrhage, hemodynamic instability or unstable airway.

Enhanced Elimination

It is indicated in patients having decreased elimination of the toxin like in renal failure where the toxin is mainly excreted in urine or where the toxin has a long half-life. This can be done with:

- *Multidose activated charcoal*: It helps by interrupting enterohepatic and enteroenteric circulation. After initial dose of 1g/kg, 0.25–0.5 g/kg is administered every 2–6 hours for 12 hours. It is useful in poisonings with carbamazepine, dapsone, phenobarbital, quinine, phenytoin, theophylline, long acting or enteric-coated formulations.
- *Urinary alkalinization*: It is useful for enhancing excretion of weakly acidic toxins through ion trapping in renal tubules. It is useful in poisoning with salicylate, fluoride, methotrexate, phenobarbital, 1–2 ampoules of sodium bicarbonate are given as a bolus and this is followed by an infusion of 2–3 ampoules in a liter of 5% dextrose along with potassium replacement at the rate of 150–250 mL/h. Target urinary pH is 7.5–8.0. It is important to monitor serum potassium levels as hypokalemic patient can not develop alkaline urine.
- *Urinary acidification*: It was used for phencyclidine or amphetamine toxicity, but it can precipitate rhabdomyolysis and myoglobinuria. So, it is never indicated now.
- *Hemodialysis or hemoperfusion*: Enhances the removal of substances with low protein binding, high water solubility and low molecular weight. It is useful in case of overdose or poisoning with caffeine, methanol, ethylene glycol, lithium, theophylline, salicylate, barbiturates, beta-blockers like atenolol.

Antidotes

Effective antidotes are limited in number and they are not to be used indiscriminately. It has a very limited role in the management of poisoning. Paracelsus accurately observed that all substances are potentially toxic (including antidotes), and only the dose differentiates a poison from a cure. Before giving an antidote, patient's clinical condition, laboratory results, expected effect of the toxin and the adverse effects of the antidote have to be taken into consideration. Antidotes work by one of these three ways:

1. Reduces the toxic conversion of the poison, e.g. ethanol inhibits metabolism of methanol to toxic metabolites by competing for alcohol dehydrogenase.
2. Competition at the receptor site, e.g. naloxone in opioid poisoning.
3. Blocking the receptor site, e.g. atropine in organophosphorus poisoning

Various antidotes and their indications are given in Box 1.

The approach to the poisoned patient has been summarized in the algorithm below.

In the emergency, the management of many things goes on simultaneously and a team doctors and paramedic staff, working in unison, would be required to take care of a critically ill poisoned patient.

by mansdocs.com

Box 1: List of antidotes and their indications.

- *N-acetylcysteine*: Acetaminophen, carbon tetrachloride
- *Ethanol*: Methanol, ethylene glycol
- *Oxygen*: Carbon monoxide
- *Naloxone*: Opioids
- *Physostigmine*: Anticholinergics
- *Atropine/pralidoxime*: Organophosphates
- *Methylene blue*: Methemoglobinemia
- *Deferoxamine*: Iron
- *BAL*: Arsenic
- *Succimer*: Lead, mercury, arsenic
- *Fab fragments*: Digoxin, colchicine
- *Glucagon*: Beta-blockers
- *Sodium bicarbonate*: Tricyclic antidepressants and other sodium channel blockers
- *Calcium/ insulin/ dextrose/ glucagon*: Calcium channel antagonists
- *Flumazenil*: Benzodiazepines

BIBLIOGRAPHY

1. Albertson TE, Dawson A, de Latorre F, et al. American Heart Association. International Liaison Committee on Resuscitation. TOX-ACLS: toxicologic-oriented advanced cardiac life support. Ann Emerg Med. 2001;37(4 Suppl):S78-90.
2. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. Position paper: ipecac syrup. J Toxicol Clin Toxicol. 2004;42(2):133-42.
3. Bardale R. Toxicolgy: general considerations. Principles of Forensic Medicine and Toxicology, 1st edition. Delhi: Jaypee Brothers Medical Publishers Pvt Ltd; 2011. pp. 413-31.
4. Boyd EM. History and general information. Predictive Toxicometries, 1st edition. Bristol: Scientechnica (publisher) Ltd; 1972. pp. 1-15.
5. Bronstein AC, Spyker DA, Cantilena LR, et al. 2008 annual report of the American Association of Poison Centers' National Poison Data System (NPDS): 26th annual report. Clin Toxicol (Phila). 2009;47(10):911-1084.
6. Brown TC, Barker GA, Dunlop ME, et al. The use of sodium bicarbonate in the treatment of tricyclic antidepressant-induced arrhythmias. Anaesth Intensive Care. 1973;1:203-10.
7. Crain EF, Gershel JC, Mezey AP. Caustic ingestions: symptoms as predictors of esophageal injury. Am J Dis Child. 1984;138(9):863-5.
8. Forget G. Epidemiological assessment of acute poisoning incidence in developing countries. Manuscript reports 219e. International Development Research Center. 1988.
9. Hoffman JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. Ann Emerg Med. 1991;20(3):246-52.
10. Ishihara K, Szerlip HM. Anion gap acidosis. Semin Nephrol. 1998;18(1):83-97.
11. Kulig K, Bar-Or D, Cantril SV, et al. Management of acutely poisoned patients without gastric emptying. Ann Emerg Med. 1985;14(6):562-7.
12. Liebelt EL, Francis PD, Woolf AD. ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. Ann Emerg Med. 1995;26(2):195-201.
13. Pillay VV. Principles of diagnosis and management. Comprehensive Medical Toxicology, 1st edition. Hyderabad: Paras Medical Publishing; 2003. pp. 8-40.
14. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. J Toxicol Clin Toxicol. 2004;42(1):1-26.
15. Srivastava A, Peshin SS, Kaleekal T, et al. An epidemiological study of poisoning cases reported to the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. Hum Exp Toxicol. 2005;24(6):279-85.
16. Voltey SR, Bosse GM, Bayer MJ, et al. Flumazenil: a new benzodiazepine antagonist. Ann Emerg Med. 1991;20(2): 181-8.

by mansdocs.com

CHAPTER

66

Specific Intoxications

Ajeet Singh, Dhruva Chaudhry

ACETAMINOPHEN

Acetaminophen is the most popular over the counter analgesic. It is the commonest poisoning in the western world especially UK. However, it is uncommon in Indian subcontinent and developing world. Acetaminophen is unique among common toxic exposures because effective treatment requires recognition of potential poisoning and initiation of therapy when no reliable clinical signs of overdose are present. The toxic dose is more than 150 mg/kg, or 8–10 grams in an average adult. Acetaminophen is primarily metabolized by liver through sulfation (20–46%) and glucuronidation (40–67%). A small percentage is oxidized to a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), by cytochrome P-450, which is quickly detoxified by hepatic stores of glutathione to a nontoxic acetaminophen—mercaptate compound that can be eliminated through renal excretion. However, during toxic overdose a larger proportion is metabolized by cytochrome P-450 to NAPQI, depleting glutathione.

Clinical Features

The evolution of acetaminophen toxicity is divided into four phases:

Phase I refers to the first 24 hours after ingestion. Patients generally remain alert but may experience nausea, vomiting, anorexia, malaise, pallor, or diaphoresis.

Phase II occurs 24–72 hours after untreated ingestion. During this period, patient may develop right upper quadrant pain and minor abnormalities of liver function consisting of elevation of hepatic enzymes, prothrombin time and bilirubin.

Phase III (72–96 hours after untreated ingestion) is characterized by continued hepatic necrosis, hepatic encephalopathy, disseminated intravascular coagulation and jaundice. Liver function abnormalities typically peak during phase III. The liver enzymes may rise to 10,000 IU/L or higher. Rare phase III sequel include hemorrhagic pancreatitis, renal failure and myocardial necrosis.

Phase IV occurs 4 days to 2 weeks after ingestion, during which recovery occurs, with return of enzymes to the normal range and without the development of chronic liver damage.

In some patients, there is a rising trend of prothrombin time, ammonia and bilirubin even though the levels of hepatic enzyme decline indicating fulminant hepatic failure.

Diagnostic Evaluation

The diagnostic evaluation consists of determining the risk of toxicity and assessing for it. The serum APAP concentration is used to predict toxicity after acute overdose. If the N-acetyl-para-amino-phenol (APAP) concentration between 4 hours and 24 hours after ingestion falls on or above the acetaminophen treatment nomogram line, the patient should be considered at risk for hepatotoxicity, and hence, in need of antidotal therapy. Conversely, if the APAP concentration is even slightly below the nomogram line, the risk of hepatotoxicity is negligible and antidotal

by mansdocs.com

therapy is not necessary. The original Rumack-Matthew nomogram line, which defined the risk of toxicity based on the natural course of untreated patients, was actually 25% higher than the line now usedin the United States. Hence, the nomogram has a 25% safety margin that allows one to be fairly rigid when using the nomogram to make treatment decisions.

In assessing the patient who is found to be at risk for toxicity and hence requires hospitalization and antidotal treatment, a complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, prothrombin time, aminotransferase levels, and bilirubin should be obtained at admission and repeated every 24 hours until resolution of toxicity is noted. If liver failure develops, laboratory values, particularly prothrombin time and glucose, must be obtained more frequently. Renal function, acid-base status, amylase and electrocardiogram may also need to be evaluated or repeated. Assessment of renal, pancreatic and myocardial toxicity should follow the same guidelines as those for other etiologies.

Treatment

Charcoal should be given within 4 hours of ingestion. Administration of N-acetylcysteine (NAC) and charcoal should, if possible, be separated by 1–2 hours to minimize any potential interactions. One must treat if the serum acetaminophen level is above the nomogram line. If gastric lavage is necessary it should be followed by a dose of charcoal. Ipecac is not recommended for home or hospital use because emesis may prevent the administration of charcoal and complicate subsequent therapy with NAC, which can itself cause vomiting. If the precise time of ingestion is unknown, then a lower threshold of 100 µg/mL at 4 hours may be taken for treatment. Treatment with N-acetylcysteine is most effective if started within 8 hours of ingestion.

Two treatment regimens are approved for treatment of acetaminophen poisoning. The first consists of a 72-hour course of oral NAC given as a 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours beginning 4 hours after the loading dose, for a total NAC dose of 1,330 mg/kg. The second regimen, approved by the Food & Drug Administration (US) (FDA) in 2004, consists of an intravenous (IV) loading dose of acetylcysteine of 150 mg/kg in 200 mL dextrose 5% in water (D_5W) over 15 minutes, followed by 50 mg/kg in 500 mL D_5W over 4 hours, then 100 mg/kg in 1 L D_5W over the next 16 hours.

AMPHETAMINE AND COCAINE

Cocaine and amphetamines are widely abused sympathomimetics for their euphorigenic and stimulant properties. Both drugs may be smoked, snorted, ingested, or injected. Amphetamines and cocaine produce central nervous system (CNS) stimulation and a generalized increase in central and peripheral sympathetic activity. Patients taking sympathomimetics in the prescribed therapeutic dose rarely develop acute sympathomimetic toxicity. Life-threatening toxicity is much more common in drug abusers and people who overdose with suicide intent. Amphetamines increase the concentration of synaptic norepinephrine by increasing norepinephrine release from presynaptic cytoplasmic and vesicular stores. The toxic dose of each drug is highly variable and depends on the route of administration and individual tolerance. The onset of effects is most rapid after IV route or smoking. Amphetamine derivatives and related drugs include methamphetamine (crystal myth, crank) Methylenedioxymethamphetamine (MDMA) (ecstasy), ephedrine (herbal-ecstasy), and methcathinone (cat).

Toxic effects of cocaine stem from excessive CNS stimulation and inhibition of neuronal uptake of catecholamine. Sympathomimetic toxicity tends to consistently result in a group of signs and symptoms known as the sympathomimetic syndrome or toxidrome, including hypertension, tachycardia, tachypnea, hyperthermia, diaphoresis, mydriasis, hyperactive bowel sounds, agitation, anxiety, and toxic psychosis. Muscle hyperactivity may lead to metabolic acidosis and rhabdomyolysis. In severe intoxication, seizures and hyperthermia may occur. Sustained or severe hypertension may result in intracranial hemorrhage, aortic dissection, or myocar-dial infarction. Hyponatremia has been reported after MDMA use. Respiratory complication include status asthmaticus, upper airway obstruction, pulmonary hypertension, barotrauma, pulmonary edema, and alveolar hemorrhage. Acute sympathomimetic intoxication in pregnant patients has been associated with abruptio placentae and spontaneous abortions.

Diagnostic Evaluation

The diagnosis is supported by finding amphetamines, cocaine, or the cocaine metabolite benzoylecgonine in the urine. Blood screening is generally not sensitive enough to detect these drugs. Those with abnormal vital signs or mental status should have an electrocardiogram, complete

by mansdocs.com

blood cell count, electrolyte, blood urea nitrogen, creatinine, glucose, creatine phosphokinase and arterial blood gas determinations.

Treatment

Patients with potential for or who have life-threatening effects from sympathomimetic toxicity, like acute coronary syndrome, myocardial infarction, multisystem organ failure and rhabdomyolysis, should be managed in an intensive care unit. These patients should receive supplemental oxygen, have vascular access established, and have their vital signs and cardiac rhythm continuously monitored.

Whole-bowel irrigation with isotonic polyethylene glycol may aid in gastrointestinal (GI) decontamination when body packing or body stuffing is suspected. Some clinicians advocate administering polyethylene glycol solution, 1–2 L/hr, to adults until the rectal effluent is clear, there is no longer radiographic evidence of drug packets in the GI tract, there is an accurate accounting of the number of ingested packets, and there is no longer significant concern for retained packets in the GI tract. Administration of multiple doses of cathartics is not considered whole-bowel irrigation and may result in severe fluid and electrolyte abnormalities.

Hemodynamic effects of sympathomimetics usually do not require specific treatment. Rapidly lower the body temperature in patients who are hyperthermic. Treat agitation, psychosis, or seizures with a benzodiazepine such as lorazepam, 2–3 mg intravenously. Add phenobarbitone 15 mg/kg intravenously for persistent seizures. Hypertension should be treated with a vasodilator agent such as phentolamine (1–5 mg intravenously) or a combined alpha and beta blocker such as labetalol (10–20 mg intravenously). A pure beta blocker such as propranolol should not be used as it may result in paradoxical worsening of hypertension due to unopposed alpha adrenergic effect. Tachycardia or tachyarrhythmias should be treated with a short acting beta blocker like esmolol (25–100 mcg/kg/min by IV infusion).

The risk of acute tubular necrosis may be minimized by maintaining urine output of at least 2–3 mL/kg/hour. Hemodialysis is indicated in patients with acute renal failure as per standard criteria. Although urinary acidification can increase the urinary excretion of some sympathomimetic drugs like amphetamine, the risks associated with urinary acidification outweigh its potential benefits.

ALUMINUM AND ZINC PHOSPHIDE

Aluminum and zinc phosphide are highly toxic insecticides and rodenticides commonly used as solid fumigants and grain preservatives. Aluminum phosphide is a very common cause of poisoning in north-west and central India. Typically, each pellet contains 3 g of 56% aluminum phosphide and 44% ammonium carbonate. Aluminum phosphide has become one of the most common suicidal agents in India and other developing countries. As little as 0.5 g can be fatal to an adult.

Toxicity of aluminum phosphide is due to phosphine which is released when it comes in contact with moisture or hydrochloric acid. The exact mechanisms of toxicity have not been elucidated; the most likely mechanism is related to noncompetitive inhibition of cytochrome c oxidase and acts by preventing the uptake of oxygen by mitochondria. Clinically, a myriad of symptoms are produced by ingestion of aluminum phosphide. Immediately after ingestion all patients develop nausea, vomiting, retrosternal burning, and in case of significant poisoning hypotension and shock. Oliguria develops in a few patients. Adult respiratory distress syndrome develops in patients with severe intoxication. Most patients develop myocarditis manifested by variable ECG changes ranging from bradyarrhythmias to tachyarrhythmia. Other complications include disseminated intravascular coagulation, intravascular hemolysis, congestive cardiac failure, hepatic failure and rarely pericarditis. Patients generally remain conscious till cerebral anoxia due to shock supervenes, resulting in drowsiness, delirium and coma. Mortality rates vary from 38% to 77% in suicidal ingestions.

Management

The diagnosis is made by history of ingestion. The diagnosis may be suggested from a decaying fish odor released by substituted phosphines and diphosphines. Silver nitrate impregnated paper blackens in the presence of phosphine in the gastric fluid.

Airway, breathing and circulatory support are important in the immediate management. Activated charcoal should be mixed with sorbitol or magnesium citrate, rather than plain water, to reduce further liberation of phosphine in the GI tract. Lavage with sodium bicarbonate (3–5% solution) or antacid has been advocated. Cardiac monitoring and ECG should be performed in suspected phosphine toxicity. Respiratory status should be monitored

by mansdocs.com

by continued clinical evaluation. Hypomagnesemia and hypermagnesemia have been reported with aluminum phosphide poisoning. Chest radiography, pulse oximetry and arterial blood gases should be obtained as clinically indicated. There is no antidote for phosphine poisoning. The mainstay of therapy is supportive care. Although IV magnesium therapy has been successful in treating various dysrhythmias, it has not been uniformly effective. Magnesium therapy in phosphide poisoning should be considered in patients with dysrhythmias or hypomagnesemia. Though corticosteroids have been administered, the outcome remains poor. Role of Intra-aortic balloon pumping has not shown any promising effects in treating refractory hypotension in these patients.

CARBON MONOXIDE (CO) POISONING

Carbon monoxide poisoning is seen regularly in clinical practice. It is one of the leading cause of unintentional poisoning death in India. Precise incidence of CO toxicity in developing countries is not available. Nonfatal incidences far outweigh fatal one and misdiagnosis is common. CO poisoning occurs as a result of exposure to internal combustion engines in ill ventilated places, fires and associated smoke inhalation and industrial accidents. Incidence tends to increase during winter months.

Pathophysiology

Carbon monoxide has 220 times more affinity to hemoglobin (Hb) than oxygen. It binds reversibly to Hb and its dissociation curve runs parallel to oxygen dissociation curve, however they move in opposite directions, i.e. CO curve shifts to right whereas oxygen dissociation curve shifts to left resulting in significant tissue hypoxia. It also has higher affinity to myoglobin thereby enhancing myocardial ischemia. CO leads to activation of platelets and neutrophil as well as free oxygen radical injury and lipid peroxidation in tissues predominantly in nervous tissue. Therefore, it is not surprising that presenting symptoms of CO toxicity are predominantly neurological and cardiovascular.

Clinical Features

Symptoms of toxicity are variable and nonspecific. Careful history of exposure is important. Commonly patient's complaint of fatigue, nausea, vomiting, dizziness and headache. As the severity increases they develop ataxia, nystagmus and impaired judgments, and become unconscious. They can also develop dysrhythmia, myocardial dysfunction leading to hypotension and metabolic acidosis. Retinal hemorrhage though uncommon if present strongly indicates CO poisoning. Patients can also have cyanosis and cherry red color of the skin. In pregnant patients, there is an increase risk of fetal death. Later on patients may develop either persistent or delayed neurologic sequelae.

Diagnostic Evaluation

The diagnosis is confirmed by CO oximetry of the blood which shows elevation of carboxyhemoglobin (COHb) levels beyond 10%. Severe poisoning is usually associated with levels more than 40%. Pulse oximeter usually gives falsely high values of saturation and must not be relied on in CO toxicity.

Treatment

First of all patient must be removed from the environment. Rescuer must take all precautions before evacuation. If person is not unconscious, then 100% oxygen with a tight mask with a flow rate of at least 10 lpm should be given. In case the patient is unconscious, he should be intubated and ventilated with 100% oxygen till COHb level reaches 5%. Where ever facility exists/available hyperbaric oxygen should be preferred in severely poisoned cases.

INSECTICIDE POISONING (ORGANOPHOSPHATES, CARBAMATE, ORGANOCHLORINE, HERBICIDE)

There are two major classes of insecticides in usage in commercial agriculture and home gardening, the Organophosphates (malathion, parathion) and the Carbamate (carbaryl, aldicarb). Insecticides can be absorbed from mouth, skin, conjunctiva, GI tract and/or respiratory tract. In many countries in which there are limited regulations on pesticide usage, pesticide ingestion is one of the leading forms of suicide, and pesticide exposure is a major occupational risk. The cause of poisoning varies from suicidal attempt to accidental exposure. Signs and symptoms of acute poisoning generally occur within first 12–24 hours after exposure.

by mansdocs.com

Organophosphate Poisoning

Commonly used organophosphates include malathion, parathion, chlorpyrifos, dichlorophos and phorate. Inhibition of acetylcholinesterase allows the neurotransmitter acetylcholine to accumulate and remain active in the synapse, resulting in sustained depolarization of the postsynaptic neuron. This effect occurs in the CNS as well as at muscarinic sites in the peripheral nervous system, nicotinic sites in the sympathetic and parasympathetic ganglia, and nicotinic sites at the neuromuscular junction. In general, effects at muscarinic sites are sustained, whereas nicotinic sites are stimulated and then depressed (hyperpolarization block). Signs and symptoms of cholinergic toxicity typically appear when 50–60% of cholinesterase activity has been inhibited.

Organophosphates bind irreversibly to cholinesterase, thus inactivating the enzyme through the process of phosphorylation. The aging that is permanent binding of the organophosphates to the enzyme requires 24–48 hours to occur. Once aging occurs only new enzymatic resynthesis must occur over a period of weeks before the clinical symptoms resolve and normal enzymatic function returns. Signs and symptoms usually begin minutes to hours after exposure.

Clinical Features

One mnemonic used to describe the cholinergic toxidrome is DUMBELS (diarrhea, urination, miosis, bronchospasm, emesis, lacrimation, salivation). In general, if signs and symptoms begin more than 12 hours after exposure, etiology is unlikely to be cholinesterase inhibitors. However, clinical effects may be delayed with lipophilic compounds (e.g. fenthion, dichlofenthion and leptophos) when ingested or after prolonged dermal exposure, leading to accumulation of a toxic dose over time. Onset may also be delayed in those organophosphorus compounds that require hepatic metabolism to a more toxic intermediate (e.g. parathion is metabolized to paraoxon). Progressive or prolonged symptoms raise the suspicion of continued absorption of the poison. Miosis may be the most sensitive marker for exposure to a cholinergic agent. Lacrimation, rhinorrhea, salivation, and profuse sweating are common in moderate to severe poisoning.Diarrhea and vomiting are seen almost universally with severe anticholinergic poisoning. Patients may present with substantial abdominal pain from vigorous intestinal contraction. Spasm of the sphincter of Oddi can lead to pancreatitis. The most frequent cause of death in cholinesterase inhibitor poisonings is respiratory failure.

An intermediate syndrome or type II toxicity has been observed to affect 5–10% of patients after the initial serious cholinergic crisis. This syndrome has been almost exclusively described in India and Sri Lanka, and may represent a genetic pattern of either neurologic response or metabolism of certain organophosphates, or an interaction of nutritional status with the toxin. The organophosphorus agents that have been associated with this syndrome are lipophilic, high-potency agents (e.g. fenthion) and may represent prolonged absorption and redistribution or delayed elimination of the organophosphate from tissue depots. Some clinicians suspect that the intermediate syndrome represents partially treated organophosphate toxicity because the syndrome appears to be predominately reported from countries with limited supplies of oximes. Only a few cases of intermediate syndrome have been reported from the Western countries, possibly related to early and aggressive use of oxime therapy. The patient appears to be recovering from acute poisoning when this manifests. An early clinical indication of this syndrome is that affected patients are unable to lift their heads up from their beds. Clinically, there is paralysis of neck flexor muscles, muscles innervated by cranial nerves, and proximal limb and respiratory muscles to the extent that some patient may require respiratory support. Deep tendon reflexes are either absent or markedly diminished. EMG may assist in diagnosis by indicating a problem at neuromuscular junction. Symptoms usually resolve within 4–18 days.

In addition to these acute effects, some organophosphate compounds can cause a delayed peripheral neuropathy (organophosphorus-induced delayed peripheral neuropathy, or OPIDN), which appears to be mediated by a membrane-bound specific neuropathy target esterase. Peripheral neuropathy is characterized by paresthesias, but motor dysfunction is more prominent, particularly foot drop and the consequent high-stepping gait. Symptoms develop slowly and can be divided into three phases: progressive, stationary and improvement.

Diagnostic Evaluation

In most of the developing countries diagnosis of OP poisoning is clinical. However, it can be confirmed by the assays of plasma and red blood cell (RBC) cholinesterases. Plasma cholinesterase assays are more readily available

by mansdocs.com

though estimation of RBC cholinesterases is preferred over serum cholinesterases. Serum and RBC cholinesterase are usually depressed at least 50% below baseline in severe intoxication. RBC cholinesterase varies by 10% on repeated testing in the same individual. It regenerates at 0.5–1.0% per day based on production of new RBCs. Thus, RBC cholinesterase may take a couple of months to return to baseline after a severe poisoning with an irreversible cholinesterase inhibitor such as an organophosphate.

Treatment of Organophosphate Poisoning (OP)

Primarily treatment of OP poisoning includes decontamination, supportive therapy including mechanical ventilation and definitive therapy in the forms of antidotes like atropine and oximes.

Decontamination: OP compounds are highly lipophilic and are readily absorbed from skin, gut and lungs. Clothes should be removed and patient should be given a thorough wash with soap and water. Gastric lavage is done routinely but is not of great help. Activated charcoal single or multiple doses though found to be effective in animal models of OP poisoning and used routinely, preferably within first hour, is not effective in humans. Airway protection should be a routine whenever lavage is done.

Supportive therapy: Large proportion of these patients develops respiratory failure secondary to depolarizing muscle paralysis and overwhelming bronchorrhea. Airway must be protected early (preferably rapid sequence) followed by control of breathing and circulation. Oxygenation should be started with an aim to have saturations more than 90%. Threshold for initiation of mechanical ventilation should be low. In case of seizures preferred treatment is benzodiazepines (Lorazepam/Diazepam/Midazolam in usual doses) along with atropine.

Respiratory muscle weakness may persist and causes difficulty in weaning, in spite of apparent improvement in general condition and resolution of symptoms. Therefore, during weaning from ventilator or otherwise in wards patients need close observation especially of respiratory and heart rate. Fall in SpO_2 or rise in $PaCO_2$ are late signs.

Specific Therapy

Atropine is the specific antidote in organophosphate poisoning. It is usually given in 2–5 mg IV bolus (0.05 mg/kg IV in children). Escalate (double) dose every 3–5 minutes until bronchial secretions and wheezing stops. Once the patient is fully atropinized, i.e. heart rate is more than 80 and secretions are dry; atropine infusion is set up by giving every hour 20–30% of the total amount that was required to atropinize the patient initially. The infusion dose is maintained for 2–3 days maintaining the full atropinization, then the infusion dose is daily reduced by 1/4th to 1/3rd of the previous day's dose. Atropine is associated with anticholinergic side effects including psychosis. Aim of the therapy is to have heart rate more than 80 with drying of secretions and not dilatation of pupils and gut paralysis (observe abdominal sounds). Glycopyrronium bromide (Glycopyrrolate) can be used in place or together with atropine or if CNS side effects of later develop.

Oximes: Theoretical and experimental basis of the use of oximes in OP poisoning are strong. In humans especially in self-harm, the data for their use is conflicting. It has been argued that efficacy of oximes depends not only on the amount but also on the nature of compound consumed (dimethyl vs diethyl, former being more resistant), dosages, time of their administration, aging and reactivation kinetics implying there is a therapeutic window during which oximes may be effective. The window in turn depends on extent and rate of aging of acetylcholinesterase. Further the type of oxime used is also a decisive factor in addition to their dosage (Obidoxime is 9 times more active than Pralidoxime). Oximes have their own side effects too. Rapid administration of oxime can cause respiratory arrest in patients having shallow respiration. In the presence of OP compounds they get converted into stable phosphoryl oximes. This further leads to the restriction of their ability to reactivate phosphorylated cholinesterase's and have been blamed for the variable response of oximes in OP toxicity.

The current evidence is unclear on the effectiveness and use of organophosphates, therefore presently it is difficult to contradict the World Health Organization (WHO) guidelines to give high dose oximes in OP poisoning. As of today the recommended dosages are—pralidoxime chloride 30 mg/kg bolus followed by 8–10 mg/kg/hr, or obidoxime 250 mg bolus followed by 750 mg/24 hrs, until at least 12 hours after stopping of atropine.

Carbamate Poisoning

Carbamates are cholinesterase inhibitors that are structurally related to the organophosphates. Commonly used carbamates are Sevin, Baygon, Lannate, etc. These transiently and reversibly inhibit cholinesterase enzymes

by mansdocs.com

unlike organophosphates. Regeneration of the enzyme occurs within few hours by dissociation of the carbamyl-cholinesterase complex. Clinical features of carbamate poisoning are similar to organophosphate poisoning but are of shorter duration. Carbamates do not penetrate the CNS readily and hence less CNS effects are seen.

Treatment

Cholinesterase levels and thus enzymatic activity usually returns to normal within 4–6 hours therefore measurement of RBC cholinesterase level is not useful. Initial treatment is similar to organophosphate poisoning. Atropine is the antidote of choice and is administered for muscarinic symptoms as is done in OP poisoning. Use of 2-PAM in carbamate poisoning has not been advocated and should be avoided.

Organochlorine Poisoning

Organochlorine compound includes dichlorodiphenyltrichloroethane (DDT), chlordane, hexachlorocyclohexane, aldrin, etc. Organochlorines are well absorbed on ingestion by inhalation and minimally through skin. The serum half-lives of these chemicals are long, varying from days to months, because of their high lipid solubility. This allows these agents to be stored in fatty tissues (e.g. brain and kidney) with the resultant delay in total body clearance. The organochlorines are known to concentrate in breast milk and fetal tissue.

Mechanism of Action

These agents are CNS stimulants and work by inhibiting gamma-aminobutyric acid and glycine pathways. This leads to inhibition of chloride channel preventing influx of Cl^- resulting in neuroexcitation, i.e. inhibitory control is lost.

Clinical Features

Symptoms are predominantly neurologic ranging from hyperexcitability, irritability, delirium, myoclonus, and facial paresthesias in mild toxicity to seizures and status epilepticus in severe toxicity. Seizures have also been reported in occupational surveys among sprayers and applicators of aldrin and dieldrin. As little as two total body applications on two successive days of 1% lindane, a common scabicide, resulted in seizures in an 18-month-old child. The peak concentration of lindane occurs 6 hours after dermal application but delayed and prolonged manifestations of toxicity may occur from dermal absorption. In addition, these agents may produce myocardial irritability with ventricular fibrillation.

Diagnostic Evaluation

History is important for making the diagnosis. Laboratory evaluation is generally not helpful but these agents can be detected in serum and urine. Serum and urine levels of these organochlorines are commonly measured by gas chromatography/mass spectrometry.

Treatment

The role of gastric decontamination depends on the clinical presentation. Immediately after an intentional ingestion and in asymptomatic patients without spontaneous emesis, gastric aspiration should be carefully performed with a small nasogastric tube. Activated charcoal should be administered soon after ingestion (preferably within 1 hour) because it can limit further gut absorption and enhance elimination by interrupting enterohepatic/enteroenteric circulation. Cholestyramine may also interrupt enteric circulation and enhance elimination. In a controlled trial, cholestyramine was administered as 16 g per day to symptomatic factory workers exposed to chlordane. After 5 months, chlordane fecal elimination was shown to increase by 3.3–17.8 times, with neurologic symptoms improving as levels declined. Milk- and oil-based cathartics should be avoided because their high lipid solubility can enhance gut absorption. Hemodialysis is not effective in enhancing elimination of these chemicals because of their high volume of distribution and protein binding. Hemoperfusion is probably of no benefit.

Organochlorine-induced seizures should be managed with benzodiazepines and barbiturates. Phenytoin may be less effective as an anticonvulsant than barbiturates and may actually increase the incidence of these seizures. For uncontrolled status epilepticus, muscle paralysis and general anesthesia may be necessary. Aggressive seizure control is warranted to limit further development of CNS damage, metabolic acidosis, hyperthermia, rhabdomyolysis, and myoglobinuric renal failure.

Respiratory distress due to bronchospasm is managed with humidified oxygen and nebulized bronchodilators. After appropriate decontamination, asymptomatic patients with an oral exposure can be observed for 6 hours and then discharged if their clinical status remains

by mansdocs.com

unchanged. Patients presenting with cardiovascular, CNS, or persistent respiratory manifestations should be admitted for further therapy and observation.

BIPYRIDYL COMPOUND

Paraquat and diquat are nonselective herbicide included in this class. Ingestion is responsible for maximum paraquat related deaths. Paraquat is distributed to most organs with maximum concentration in lungs and kidneys. Acute exposure causes liver and renal necrosis that is followed in weeks by pulmonary fibrosis. Paraquat accumulates in the alveolar cells of the lungs where it is transformed to reactive oxygen species, the superoxide anion. This anion is responsible for lipid peroxidation causing degradation of the membranes. Paraquat and oxygen enhance each other's toxicity by sustaining the redox cycle. Myocardial injury and necrosis of adrenal gland may occur. Paraquats caustic effects cause local skin irritation and ulceration of the mucous membranes. Hypovolemia occurs due to GI loses and decreased oral intake. Cardiovascular collapse may occur early in severe toxicity. Multisystem effects then occur including GI corrosion, acute tubular necrosis and extensive pulmonary injury. Seizures, GI perforation and hemorrhage and hepatic failure may occur. Pulmonary fibrosis leading to refractory hypoxemia occurs 5 days to several weeks later. Metabolic (lactic) acidosis is common as a result of pulmonary effects (hypoxemia) and multisystem failure.

Treatment

Early diagnosis and treatment are essential. Diagnosis is based up on history. Qualitative and quantitative analyses for paraquat in serum and urine can help in diagnosis. A 10-hour level of greater than 0.4 mg/L carries a high probability of death. The goal of early and vigorous decontamination is to prevent pulmonary toxicity. Early treatment is supportive. An attempt should be made to prevent superoxide radical formation by using low inspired oxygen to produce a therapeutic hypoxemia with the goal of reducing pulmonary toxicity. The use of low oxygen mixtures [fraction of inspired oxygen (FiO_2) <21%] with positive pressure ventilation reduces pulmonary toxicity. It is suggested that a higher FiO_2 may only be used when arterial oxygen pressure is less than 40 mm Hg. Maintaining intravascular volumes and urine output is important to prevent prerenal failure. Immediate gut contamination with activated charcoal must be done. Immunosuppressive therapy (cyclophosphamide with dexamethasone) has shown possible benefit in anecdotal reports.

OPIOIDS

The term Opioids is an all-inclusive term for antagonists, endogenous and exogenous substances that possess morphine like activity. The most commonly abused opioids are heroin and methadone. Prescription and illicit opioids (morphine, codeine, oxycodone, fentanyl, etc) are popular drugs of abuse and the cause of frequent hospitalizations for overdose. These drugs have widely varying potencies and durations of action; some of the illicit fentanyl derivatives are up to 2,000 times more potent than morphine. Natural opioids (e.g. morphine and codeine) are found in opium, harvested from the seed pods of the poppy plant *Papaver somniferum*.

Clinical Features

A typical morphine dose (5–10 mg) usually produces analgesia without altering mood or mental status in a patient. The clinical effects of morphine are accentuated with increasing doses (e.g. analgesia is stronger, lethargy and drowsiness progress to sleepiness and coma). Slurred speech and significant motor incoordination are usually absent. All of these agents decrease CNS activity and sympathetic outflow by acting on opiate receptors in the brain. Mild intoxication is characterized by euphoria, drowsiness and constricted pupils. More severe intoxication may cause hypotension, bradycardia, hypothermia, coma and respiratory arrest. Pulmonary edema may occur. Respiratory failure is the most serious consequence from opiate overdose. Opioid agonists reduce the sensitivity of the medullary chemoreceptors in the respiratory centers to an increase in carbon dioxide tension and depress the ventilatory response to hypoxia. Death is usually due to apnea or pulmonary aspiration of gastric contents. Methadone has been associated with QT interval prolongation and torsades de pointes. With meperidine, the metabolite normeperidine probably causes seizures and is most likely to accumulate after repeat dosing in patients with chronic kidney disease. Propoxyphene is structurally related to methadone. It is available alone or in combination with aspirin or acetaminophen. Propoxyphene toxicity has resulted in significant morbidity and mortality. Oral administration is followed by rapid absorption, with peak serum levels

by mansdocs.com

occurring in 1 hour. The clinical course after propoxyphene overdose may be severe and rapidly progressive, with cardiac dysrhythmias, circulatory collapse, seizures, and respiratory arrest developing within 45 minutes.

Treatment

A diagnosis of opioid poisoning should be considered in all comatose patients. However, the classic triad of opiate toxicity (coma, miosis and respiratory depression) may not be apparent after a mixed overdose. Respiratory support is paramount in the management of patients with opioid toxicity; one should secure the airway and ventilate with 100% oxygen. Vascular access should be established. The patient should be placed on continuous pulse oximetry and cardiac monitoring. Vital signs should be monitored frequently.

Naloxone is a specific opiate-receptor antagonist and can reverse the analgesia, respiratory depression, miosis, hyporeflexia, and cardiovascular effects of opiate toxicity. It is also effective in terminating opioid-induced vomiting. The goal of naloxone therapy is to re-establish adequate spontaneous ventilation. The initial IV naloxone dose should be 0.1 mg if the patient is possibly opioid-dependent; larger doses may precipitate acute opioid withdrawal syndrome. Otherwise, an initial 2-mg dose can be administered. Very large doses (10–20 mg) may be required for patients intoxicated by some opioids (propoxyphene, codeine, fentanyl derivatives). The duration of effect of naloxone is only 2–3 hours and repeated doses may be necessary for patients intoxicated by long-acting drugs such as methadone. A therapeutic continuous naloxone infusion can be made by multiplying the effective naloxone bolus dose by 6.6, adding that quantity to 1,000 mL normal saline, and infusing the solution at 100 mL per hour. The infusion is titrated to maintain adequate spontaneous ventilation without precipitating acute opioid withdrawal and is empirically continued for 12–24 hours. The patient should be admitted to an intensive care or high-dependency setting for continuous monitoring. After the naloxone therapy is discontinued, the patient should be carefully observed for 4 hours for recurrent respiratory depression. Management of seizures should follow present treatment guidelines and should include benzodiazepines or barbiturates. Adjunct naloxone therapy may be effective in propoxyphene but not meperidine- or tramadol-related seizures.

Gastrointestinal decontamination should be considered after vital signs have been stabilized. Gastric lavage is rarely useful but may benefit patients who do not respond to naloxone, those suspected of polypharmacy overdose, or those who overdosed on diphenoxylate. Early administration of activated charcoal has been advocated as the sole GI decontamination procedure. Patients should be closely monitored for the presence of bowel sounds and passing of charcoal-laden stool. Repeat charcoal doses should not be used in the absence of active bowel sounds or in the presence of an ileus. Ipecac-induced emesis has no role in patients with opioid overdose.

Nalmefene is also effective for the reversal of opioid-induced CNS effects and can be administered orally or intravenously. Its half-life and dose-dependent duration of action are 4–8 hours after IV administration. The initial adult dose is 0.5 mg for those who are not opioid-dependent and 0.1 mg for those suspected of having opioid dependency. If there is an incomplete response or no response, additional doses can be given at 2- to 5-minute intervals. A total dose of 1.5 mg may be necessary to exclude the possibility of opioid poisoning. Nalmefene has proven safety and efficacy in the management of meperidine-induced sedation and opiate overdose. The principal advantage over naloxone is its considerably longer duration of antagonistic action, which translates into fewer complications arising from fluctuations in the level of consciousness, reduced incidence of resedation, better long-term control of longer-acting opiate ingestions, and fewer indications for naloxone infusions. Withdrawal syndrome precipitated by the use of nalmefene would also be prolonged.

Naltrexone is a potent, long-acting pure opiate antagonist that is effective orally. Its use is primarily limited as adjunctive therapy for opioid detoxification. Naltrexone may induce a withdrawal syndrome that lasts up to 72 hours.

ALCOHOL POISONING

The accidental or deliberate consumption of alcohols and glycols is a major cause of health problems in India and abroad. Ethyl alcohols and glycols, especially methanol and ethylene glycol, can be far more toxic after acute exposure. Ethanol is an aliphatic alcohol, a small, slightly polar, molecule with a weak electric charge, miscible in water and lipids. It diffuses easily into all body tissues. It is postulated that ethanol influences multiple ion channels, possibly by causing subtle alterations in their tertiary structure or their dynamic interaction with cell membranes.

by mansdocs.com

ETHANOL POISONING

Ethanol is readily absorbed from the GI tract, with 80% of the absorption occurring in the small intes-tine. Peak ethanol levels typically occur 30–60 minutes after ingestion if the stomach is empty. Women have higher peak ethanol concentrations after a given dose because of smaller body mass and smaller relative body water, rather than reduced first-pass metabolism due to gender differences in gastric mucosal alcohol dehydrogenase (ADH) activity.

Metabolism of ethanol occurs predominantly in the liver by three enzymatic systems: The cytosolic ADH enzyme, the cytochrome P450 enzyme and peroxisomal catalase. Only a small fraction of ethanol is exhaled or secreted in urine and sweat.

Alcohol dehydrogenase is responsible for greater than 80% of ethanol metabolism at lower doses. In the ADH metabolic pathway ethanol is oxidized to acetaldehyde and then to acetate in a process that reduces oxidized nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide (NADH). The increased ratio of NADH to NAD^+ can inhibit NAD^+-dependent reactions, such as gluconeogenesis, as well as slowing subsequent ethanol oxidation and clearance. Acetate undergoes conversion to acetyl coenzyme A (CoA), which can then participate in the citric acid cycle, fatty acid synthesis, or ketone formation. Genetic variations in ADH and aldehyde dehydrogenase have been extensively characterized and may play a role in determining susceptibility to alcoholism.

Gross motor control and orientation may be significantly affected, and clinical ethanol intoxication may become apparent at concentrations of 50 mg/dL. Lethargy, ataxia and muscular incoordination may be seen at serum levels of 150 mg/dL or greater, coma at approximately 250 mg/dL, and death with levels greater than 450 mg/dL. Tolerant drinkers can achieve higher levels before developing similar symptoms, and survival has been reported despite a serum level of 1500 mg/dL. At high doses, ethanol functions as an anesthetic, causing CNS depression, autonomic dysfunction (e.g. hypotension, hypothermia), coma, and death from respiratory depression and cardiovascular collapse. The estimated lethal dose 50% or median lethal dose in adults is 5–8 g/kg, and 3 g/kg for children.

Diagnostic Evaluation

In patients with moderate to severe poisoning, laboratory studies should include complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, glucose, ethanol, magnesium, calcium, and phosphorus level, liver function tests, prothrombin time, electrocardiogram, chest radiograph, arterial or venous blood gas, and urinalysis. Further studies should be obtained as clinically indicated. If the level of consciousness is inconsistent with the serum ethanol level or does not improve over a few hours, the physician should reconsider the diagnosis of ethanol intoxication.

Treatment

Patients with stupor or coma who cannot be aroused to a verbal (but not necessarily coherent) state should be intubated to ensure airway patency and to protect against pulmonary aspiration. Poor respiratory effort necessitates mechanical ventilatory support. IV naloxone (2 mg) and thiamine hydrochloride (100 mg) should be administered. Naloxone reverses opioid effects if they are present, whereas the thiamine may treat an underlying Wernicke's encephalopathy. If a bedside glucose test reveals hypoglycemia, IV dextrose (25–50 g) should be administered.

METHANOL POISONING

Methanol is a colorless liquid and has an odor distinct from that of ethanol. Dietary sources and endogenous metabolism can produce methanol levels of 0.15 mg/dL.

Methanol is oxidized by hepatic ADH to formaldehyde, which is quickly converted to formic acid (formate) by aldehyde dehydrogenase. In primates, formate accumulates due to saturation of one-carbon metabolism. High levels of formate, an inhibitor of mitochondrial cytochrome oxidase, cause histotoxic hypoxia and are responsible for the characteristic metabolic acidosis and ocular toxicity seen with methanol toxicity. Formaldehyde is also very toxic, but it has a very short elimination half-life. Symptoms and prognosis also correlate better with formate than with methanol levels.

Clinical Features

Onset of toxicity usually occurs within 30 hours of methanol ingestion. Factors influencing time to symptoms include the amount ingested, concomitant ethanol intoxication, and the individual's folate status. Neurologic, ophthalmologic, and GI symptoms predominate. Methanol is approximately one-half as potent as ethanol in its ability

by mansdocs.com

to cause CNS depression. Patients are frequently alert on admission and complain of headache and dizziness. Amnesia, restlessness, acute mania, lethargy, confusion, coma and convulsions may be seen. Early on, many patients offer no visual complaints. Visual symptoms accompany the metabolic acidosis and are usually experienced acutely when the blood pH is below 7.2. Patients presenting very late may have a normal blood pH after the formate has been completely eliminated. Blurred vision, photophobia, scotomata, eye pain, partial or complete loss of vision have been reported. Pupils may react sluggishly or may be fixed and dilated. Funduscopic examination may show hyperemia of the optic disks followed by retinal edema, which develops initially along the retinal vessels and then spreads to the central areas of the fundus. Retinal vessel engorgement accompanies the retinal edema.

Methanol can produce severe hemorrhagic gastritis and pancreatitis, causing upper abdominal pain, nausea, vomiting and diarrhea. Liver function abnormalities have been documented in moderately to severely ill patients.

Vital signs may reveal tachycardia and increased Kussmaul's respirations, but the blood pressure is usually maintained until death. Before the availability of current therapeutic modalities, patients died from sudden respiratory arrest. The skin may be cool and diaphoretic, and rigidity of abdominal muscles without rebound tenderness has been reported. Ophthalmologic findings do not correlate with visual complaints, but do parallel the severity of the toxicity.

Diagnostic Evaluation

Methanol can also cause an anion gap metabolic acidosis and an osmol gap. Elevated lactate levels, mild hypokalemia, and leukocytosis may occur. Serum lactate concentrations of 11.5 and 23 mmol/L have been reported 24 hours or more after ingestion. Computed tomography scanning can demonstrate cerebral edema, as well as frontal lobe and basal ganglia hemorrhages and infarcts.

Treatment

Treatment involves supportive care, antidotal therapy to block further metabolism by ADH, cofactor therapy, and other measures to enhance the elimination of the parent agent and its toxic metabolites.

Initial treatment includes airway management in the comatose patient, IV fluids, cardiac monitoring, and appropriate laboratory studies. Gastric aspiration via a nasogastric tube may be beneficial when performed within an hour of a massive ingestion. Oral activated charcoal is relatively ineffective but should be considered only when coingestants are suspected.

Intravenous sodium bicarbonate should be administered to correct serum pH to at least 7.3. Large doses of sodium bicarbonate may be required to correct lactic acidosis, increase of pH and urine alkalinization. Ethanol and fomepizole are antidotes for methanol poisoning. These agents inhibit ADH, which catalyzes the initial oxidation of methanol to their more toxic metabolites. It is indicated when serum methanol or ethylene glycol concentration more than 20 mg/dL.

DETERGENT POISONING

Detergent is a substance or preparation containing soaps and/or other surfactants intended for washing and cleaning processes. "Acute detergent poisoning is becoming increasingly common in the west due to use of detergent pods for dish washing which are accidentally ingested by children, resulting in serious complications. The American Association of Poison Control Centers (AAPCC) reported that 92% of all toxic exposures occur in the home and nearly 53% of these exposures occurred in children less than 6 years of age. Accidental poisoning with detergents can pose a significant risk especially in children and elderly but majority of the affected individuals have minimal or no side effects. These detergent products contain anionic surfactants and detergent builders such as sodium phosphates, sodium carbonate and sodium aluminosilicates, which are highly alkaline with a pH as high as 10–12. The surfactant acts on the protein of the cell membrane causing its solubilization and degeneration, causing widespread toxicity. Detergents fall into three main categories—nonionic, anionic and cationic. Nonionic and anionic detergents are of low toxicity, causing minor symptoms and only a close observation is required in most of the cases but serious symptoms and even death has also been reported. Cationic detergents, such as benzalkonium chloride and cetrimide, are less frequently encountered in domestic cleaners and produce corrosive effects if a concentrated solution is consumed.

The route of exposure is almost always oral ingestion but inhalational, ocular and dermal exposures, and even IV route. Corrosive injury to the GI, respiratory and corneal mucosa (depending on route of exposure), cardiac dysfunction, acute renal failure with rhabdomyolysis, ARDS (early and late onset), hemolysis, frequent ventricular

by mansdocs.com

tachycardia, coagulation abnormalities have been reported secondary to exposure of household detergents.

There is no standardized treatment protocol for detergent poisoning. Syrup of ipecac for gastric decontamination should not be administered, given the risk of aspiration and potential for further caustic injury to the esophagus. Patients at risk of esophageal damage require hospital admission and careful attention to fluid and electrolyte balance. Early endoscopic examination with gastric aspiration may be considered but only after airway is secured. Endotracheal intubation and supportive ventilation is required frequently. Use of nebulized racemic epinephrine and administration of corticosteroids have been used in patients with respiratory involvement with some success.

BIBLIOGRAPHY

1. Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. 2002;40(4):415-46.
2. Boyer EW, Mejia M, Woolf A, et al. Severe ethylene glycol ingestion treated without hemodialysis. Pediatrics. 2001;107(1):172-3.
3. Bumbrah GS, Krishan K, Kanchan T, et al. Phosphide poisoning: a review of literature. Forensic Sci Int. 2012;214 (1-3):1-6.
4. Calello DP, Henretig FM. Pediatric toxicology: specialized approach to the poisoned child. Emerg Med Clin North Am. 2014;32(1):29-52.
5. Ceccatelli S. Mechanisms of neurotoxicity and implications for neurological disorders. J Intern Med. 2013;273(5): 426-8.
6. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5): 745-57.
7. Goel A, Aggarwal P. Pesticide poisoning. Natl Med J India. 2007;20(4):182-91.
8. Kostic MA, Dart RC. Rethinking the toxic methanol level. J Toxicol Clin Toxicol. 2003;41(6):793-800.
9. Ozucelik DN, Karcioglu O, Topacoglu H, et al. Toxicity following unintentional DDT ingestion. J Toxicol Clin Toxicol. 2004;42(3):299-303.
10. Patel SR. Toxicologic emergencies in the intensive care unit: management using reversal agents and antidotes. Crit Care Nurs Q. 2013;36(4):335-44.
11. Proudfoot AT. Aluminium and zinc phosphide poisoning. Clin Toxicol (Phila). 2009;47(2):89-100.
12. Ramlawi M, Marti C, Sarasin F. [Paracetamol overdose]. Rev Med Suisse. 2013;9(394):1478-82.
13. Raub JA, Mathieu-Nolf M, Hampson NB, et al. Carbon monoxide poisoning—a public health perspective. Toxicology. 2000;145(1):1-14.
14. Roth B, Woo O, Blanc P. Early metabolic acidosis and coma after acetaminophen ingestion. Ann Emerg Med. 1999; 33(4):452-6.

by mansdocs.com

CHAPTER

67

Fatal Envenomations

Prashant Kumar, Dhruva Chaudhry

INTRODUCTION

Envenomation is a process by which a venomous animal injects venom into some animal by bite (or sting). Some reptiles, spiders, insects use venom for hunting and for self-defense. Mostly, venom is administered by biting the skin of the victim, but some venom is applied externally, especially to sensitive tissues.

SNAKEBITE

Epidemiology

Snakes are widely distributed on earth's surface with some exceptions such as the Arctic, Antarctic and many small islands. Snake envenomation is a common emergency seen in rural tropics. Snakebite is an occupational hazard in paddy farmers or farm workers and in rural population, with distinct seasonal variation of summer and rainy season having its high incidence when reptiles come out of their habitats. In India, approximately 81,000 snakes envenoming occur each year, which result in about 11,000 deaths. However, these numbers may be a gross underestimation of the true burden morbidity and mortality in snakebite victims.

Based on different toxicology, snakes are divided in Elapidae, the Viperidae and the Hydrophiidae. Elapidae (cobra, king cobra, krait and coral snake) and viperidae (pit vipers like rattle snake and pitless viper like Russell's viper) are predominantly toxic to humans. Sea snakes (Hydrophiidae) are found near the seacoast, though venomous, they seldom bite. The snake, if killed, should be carefully taken to the hospital for identification.

Pathophysiology of Snake Envenomation

Snake venom contains various proteins, peptides, carbohydrates and metals, which cause toxic and lethal effects on the skin, hematological, nervous, respiratory and cardiovascular systems. Release of endogenous histamine, bradykinin and adenosine compounds the toxic effects (Table 1).

Clinical Presentations

Varies with the type of snake envenomation, quantity of venom inoculated and patient general condition. Although classified into predominantly neurotoxic, hemorrhagic and myotoxic types, each species can result in any or mixed kind of manifestations.

Table 1: Snake venom components and their effects.

Component	*Viperidae*	*Elapidae*	*Action*
Enzymes			
Proteinases	Heavy	Minimal	Tissue destruction, coagulation, anticoagulation
Hyaluronidase	Moderate	Moderate	Hydrolysis of connective tissue stroma
Cholinesterase	Minimal	Heavy	Catalyses, hydrolysis of acetylcholine
Phospholipase A	Heavy		Hemolysis, may potentiate neurotoxins
Phosphoesterase	Minimal	Heavy	Unknown
Phosphodiesterase	Moderate	Moderate	Hypotension
Nonenzymes			
Neurotoxins	Minimal	Heavy	Flaccid paralysis

by mansdocs.com

Viper bite is primarily vasculotoxic. It causes rapidly developing swelling of the bitten part. Local necrosis is mainly ischemic as thrombosis blocks the local blood vessels and causes a dry gangrene. Systemic absorption is slow, it occurs via the lymphatics and leads to lymphangitis. Hemostatic abnormalities are characteristic and are the cause of the complications that lead to death. Persistent ooze from the bite mark and the site of the IV cannula is an indication of the altered clotting mechanism. Hemorrhage and increased capillary permeability lead to shock and pulmonary edema. Oliguria ensues, followed by loin pain due to renal ischemia. Renal failure is the common event.

Cobras and kraits of elapidae group produce medically significant neurotoxin and are major contributors to mortality and morbidity. The neurotoxic venom can act on either or both sites, i.e. presynaptic or postsynaptic at the neuromuscular junction. Cobra's venom at postsynaptic junction competes with acetylcholine to bind the nicotinic receptors by blocking the receptors, the signal cannot cross the neuromuscular junction thus inhibiting muscle contraction and leading to paralysis progressing to respiratory paralysis requiring ventilator support. Presynaptic venom of krait acts at the cephalad side of synaptic cleft. The venom consists of phospholipase A_2 which damages motor end plate and destroys synaptic vesicles leading to elimination of acetylcholine, causing paralysis and respiratory failure. Signs and symptoms can be compared to suspect the type of snakebite (Table 2).

Sea snake envenomation has both myotoxic and neurotoxic effects which result in clinical and pathological changes typical of segmental myopathic lesions in the skeletal muscles. Muscle pains may last for several months unless treated. Myoglobin and potassium released from damaged skeletal muscle can cause renal failure, while the hyperkalemia thus produced may lead to cardiac arrest.

Investigations

Twenty minutes whole blood clotting test (WBCT) is WHO recommended gold standard. Failure of blood to clot within 20 minutes signifies significant toxicity (glass test tube, cleaned without detergent, dry). Complete hemogram with platelet counts, bleeding time (BT) and clotting time (CT) must also be done. Urine should be examined for RBC in the absence of hematuria. Alternately where facility exists, prothrombin time index (PTI), partial thromboplastin time with kaolin (PTTK). Fibrinogen level, creatinine kinase, etc. should be done. If urine is smoky and lack RBC's myoglobulin, it should be looked into to rule out myoglobinuria. Electrolytes, blood urea and serum creatinine levels should be regularly monitored in patients with renal failure. Arterial puncture is contraindicated in coagulopathy. Hyperkalemia and hypoxemia with respiratory acidosis are seen, particularly with neuroparalysis.

Enzyme-linked immunosorbent assay (ELISA) wherever available should be done to confirm snake species.

Table 2: Signs and symptoms of snake envenomation.

General signs and symptoms of viperine envenomation	*General signs and symptoms of elapid envenomation*
• Swelling and local pain	• Swelling and local pain
• Tender enlargement of local lymph nodes	• Local necrosis and/or blistering
• Bleeding, epistaxis	• Descending paralysis, (commencing with ptosis, diplopia or ophthalmoplegia, upper airway obstruction, pooling of secretions, bulbar paralysis and respiratory failure
• Vomiting	• Cyanosis, altered sensorium and coma
• Acute abdominal tenderness	• Paradoxical respiration
• Hypotension (hypovolemia or direct vasodilation)	• Stomach pain (submucosal hemorrhages)
• Low back pain (early renal failure or retroperitoneal bleeding)	• Krait bites often present in the early morning with paralysis that can be mistaken for a stroke
• Petechiae, purpura ecchymoses	
• Reddish or dark-brown urine or oliguria/ anuria	
• Lateralizing neurological symptoms and asymmetrical pupils	
• Muscle pain (rhabdomyolysis)	
• Parotid swelling, conjunctival edema, subconjunctival hemorrhage	

by mansdocs.com

Table 3: Indications of ASV.

• Systemic envenoming	• *Evidence of coagulopathy*: Primarily detected by whole blood clotting time in 20 min (20WBCT) or visible spontaneous systemic bleeding • *Evidence of neurotoxicity*: Ptosis, external ophthalmoplegia, muscle paralysis, inability to lift the head, etc. • *Cardiovascular abnormalities*: Hypotension, shock, cardiac arrhythmia, abnormal ECG
(The first two methods of establishing systemic envenomation are the primary determinants)	• Persistent and severe vomiting or abdominal pain
• Severe current local envenoming	• Severe current, local swelling involving more than half of the bitten limb (in the absence of a tourniquet) • In the case of severe swelling after bites on the digits (toes and especially fingers), after a bite from a known necrotic species • Rapid extension of swelling (for example, beyond the wrist or ankle within a few hours of bites on the hands or feet). (Old swelling is not grounds for giving ASV).

(20WBCT: 20 min whole-blood clotting time; ASV: Anti-snake venom; ECG: Electrocardiogram).

Treatment

The first aid being currently recommended is based around the mnemonic: "Do it R.I.G.H.T." Victim should be reassured as 70% of all snakebites are from nonvenomous species. Only 50% of bites by venomous species actually envenomate. The limb should be immobilized with care not to block the blood supply or apply pressure. Victim should be asked to get to hospital immediately as traditional remedies have no proven benefit, also any systemic symptom, such as ptosis, that manifests on the way to hospital should be told.

Supportive Therapy

General measures are always to support airway, breathing and circulation.

Tetanus toxoid is to be given whenever there is evidence of a bite, where the skin has been broken.

Analgesics are required to relieve pain. Paracetamol 500–1,000 mg, 4–6 hourly is a good option. Aspirin should be best avoided.

Antibiotics should be considered if there is evidence of cellulitis or necrosis.

If patient develops bulbar palsy or has difficulty in swallowing or speaking, airway must be protected. Patient must be intubated before giving anti-snake venom (ASV) and ventilated if respiration is shallow or tachypneic.

Anti-snake Venom

Anti-snake venom is the mainstay of treatment. ASV used in India is polyvalent, i.e. it is effective against all the four common species: (i) Russell's viper (*Daboia russelii*), (ii) common cobra (*Naja naja*), (iii) common krait (*Bungarus caeruleus*) and (iv) saw scaled viper (*Echis carinatus*). There are no currently available monovalent ASVs primarily because there are no objective means of identifying the snake species, in the absence of the dead snake. ASV is produced in both liquid and lyophilized forms. Liquid ASV requires a reliable cold chain and refrigeration and has a 2-year shelf life. Lyophilized ASV, in powder form, has shelf life of 5 years and requires only to be kept cool which is therefore useful in remote areas.

Anti-snake venom administration criteria (Table 3): Anti-snake venom should only be administered when there are definite signs of envenomation. Unbound, free flowing venom can only be neutralized when it is in the bloodstream or tissue fluid. ASV has got no action to reverse the attached venom. In addition, ASV carries risks of anaphylactic reactions and should not therefore be used unnecessarily.

Dosage of anti-snake venom: The recommended dosage level has been based on published research that Russell's viper injects on average 63 mg of venom. Initial dose should be calculated to neutralize the average dose of venom injected. The range is 5–147 mg. Total required dose will be between 10 vials and 25 vials as each vial neutralizes 6 mg of Russell's viper venom. All victims will require neither 10 vials as some may be injected with less than 63 mg nor 25 vials. However, starting with 10 vials ensures that there is sufficient neutralizing power to neutralize the average amount of venom injected and during the next 12 hours to neutralize any remaining free flowing venom.

by mansdocs.com

Initial dose

- Mild envenomation (systemic symptoms manifest >3 hours after bite) neurotoxic or hemotoxic 8–10 vials
- Severe envenomation (systemic symptoms manifest <3 hours after bite) neurotoxic or hemotoxic 8 vials
- Each vial is 10 mL of reconstituted ASV.

Children versus adults: Children receive the same ASV dosage as adults. The ASV is targeted at neutralizing the venom. Snakes inject the same amount of venom into adults and children.

Further doses will depend on the response to the initial dose. ASV should be administered either as IV infusion (5–10 mL/kg body weight) or as slow IV injection (2 mL/min) at a constant speed and patient should be closely monitored for 2 hours.

In victims requiring life saving surgery, a higher initial dose of ASV is justified (up to 25 vials) solely on the presumption that coagulation will be restored in 6 hours.

Local administration of ASV near or at the bite site should not be done. It is ineffective, painful and can raise the intracompartmental pressure.

Anti-snake venom is a foreign protein prepared by immunizing horses with venom from poisonous snakes, serum extracted and purified. Anaphylaxis with ASV may be life threatening. The patient after ASV administration should be monitored closely and if anaphylaxis is evident, ASV should be discontinued. It should be followed by adrenaline: usual recommended dosage is 0.5 mg of 1:1,000 dilution s/c. Additional dosages of H_1 (chlorpheniramine maleate) and H_2 (ranitidine) blockers with hydrocortisone 100 mg, though later will take 4–6 hours to act, should be given simultaneously. If needed, adrenaline can be repeated up to 2–3 dosages or an infusion can be started in dilution of 1:50,000. Hypotension is treated with fluids additionally. Inotropes may be required in patients who had overt myocardial dysfunction.

Patients with postsynaptic envenomation are benefited with anticholinesterase such as neostigmine given with atropine (to counter muscarinic effects of anticholineastrases). 10 mg of edrophonium or 0.5 mg of neostigmine should be given over 2–3 minutes. In case patient improves, then patient should be managed with neostigmine or atropine over next 24–48 hours. Single breath count, upward gaze times are reproducible bedside tests to assess response. Paralysis is descending, starting with cranial nerves causing ptosis, diplopia progressing to bulbar paralysis, dysphagia and respiratory failure. Recovery is in opposite direction, i.e. below upward. Patients developing renal failure need hemodialysis.

SCORPION STING

Scorpion stings are common in many tropical and subtropical countries, especially Africa, South India, the Middle East, Mexico and South Latin America. There are about 1,500 scorpion species, out of which 50 are dangerous to humans. The exact data about scorpion sting deaths in India are not available, but the magnitude can be estimated by the data that in Mexico, 1,000 deaths from scorpion stings occur per year. In Maharashtra and Southwestern India the envenomation is seen entirely after stings of Mesobuthus tamulus (known as red scorpion), whereas in eastern India it is secondary to *Heterometrus bengalensis*.

The venom glands of scorpion are located on the tail lateral to the tip of the stinger. Generally, the venom is distributed rapidly into the tissue if it is deposited into a venous structure. Venom deposited via the IV route can cause symptoms only 4–7 minutes after the injection. The more rapidly the venom enters the bloodstream, the higher the venom concentration in the blood and the more rapid the onset of systemic symptoms.

Scorpion venom may contain multiple toxins and other compounds. The venom is composed of varying concentrations of neurotoxin, cardiotoxin, nephrotoxin, hemolytic toxin, phosphodiesterases, phospholipases, hyaluronidases, glycosaminoglycans, histamine, serotonin, tryptophan, and cytokine releasers. The most important clinical effects of envenomation are neuromuscular, neuroautonomic, or local tissue effects.

Unlike snake venom, scorpion venom primarily acts on gated channels primarily sodium channels leaving them open, thereby leading to constant stimulation. Venoms effect on presynaptic membranes leads to cholinergic as well as adrenergic hyperstimulation resulting in massive release of catecholamines and stimulation of angiotensin- renin axis. The autonomic storm is associated with intense vasoconstriction, cardiac stimulation with increased myocardial oxygen demand and marked metabolic abnormalities like pheochromocytoma crisis ending up in myocardial necrosis and failure. In addition, activation of cholinergic stimulation also takes place. Therefore, it is not surprising that clinical syndrome is dominated by features of autonomic crisis including severe cardiovascular effects and cholinergic stimulation.

by mansdocs.com

Clinical Features

Clinical sign and symptoms depend primarily on the amount of venom released in the body. If accidentally the venom is injected in the veins, then presentation of envenomation can occur in as little as 5–10 minutes. There occurs intense severe pain at the site of sting. It worsens on taping at the site of bite (Tap sign) and may be associated with burning and paresthesia. Systemic envenomation is characterized in the initial stages by tachycardia and hypertension. There may be sweating, lacrimation and fasciculation. In severe envenomation, patient develops pulmonary edema, dysrhythmias, hypotension that becomes refractory later. Muscle paralysis and priapism are also not uncommon to see.

Investigations

- *Electrocardiogram (EKG)*: Sinus tachycardia, QTC prolongation, ST-T changes including T inversions. AV blocks in 10–12% of patients.
- *Echo*: Global left ventricular hyperkinesis. In patients with moderate to severe toxicity, it shows the return to normal after recovery.
- *Pulmonary artery (PA) studies*: Demonstrates elevated systemic vascular resistance (SVR) which may be increased up to four times with low cardiac index and elevated filling pressures.
- *Chest X-ray (CXR)*: It may show cardiomegaly with evidence of pulmonary edema.

Biochemical: Hyperglycemia and elevated levels of free fatty acids (FFA) are common.

Coagulation parameters and blood gases should be done when necessary.

Treatment

Scorpion bite is an emergency and patients with systemic manifestation must preferably be managed in critical care units.

Local

Immobilize the affected part and keep it below heart. Lymphatic venous compression may be applied an inch proximal to prevent venom absorption. Like snake envenomation, it should be removed when one is in position to provide life sustaining support.

Pain can be relieved by giving ice packs as well as analgesics. Ice packs are most effective when applied earlier, preferably within 2 hours of sting.

Systemic

General: Primary aim is to resuscitate and stabilization. One must follow the principles of resuscitation, i.e. establish airway, breathing and circulation and shift the patient to intensive care for monitoring. Oxygen to maintain saturations more than 90%. Fluids should be administered to prevent hypovolemia, which is not uncommon in theses seriously sick patients.

Specific

Antivenin is the treatment of choice and should be administered at the first opportunity after stabilization of the patient. In India it is manufactured by Haffkine institute. Usual starting dose is 10 mL of the reconstituted ASV and can vary from 10–30 mL or more depending on the severity and evolution of toxicity. 1 mL neutralizes approximately 13–17 mg of crude venom. Antivenom neutralizes only free venom, therefore on gong toxicity may continue. Either one has to use more ASV or preferably prazosin (which is a postsynaptic alpha 2 blocker) which reveres the most of the effects of the venom.

Combination of sympathetic alpha-blocker (prazosin) with beta-blocker is most effective in reversing the effect of venom in patients who primarily have hyperdynamic cardiovascular changes manifested by tachycardia and hypertension. Beta-blockers must never be used alone. Golden rule is to treat it like pheochromocytoma crisis. Prazosin alone has decreased the mortality from 30% to 40% to less than 3%. Therefore, if ASV is not available then patient must preferably be treated with prazosin.

Insulin-glucose-potassium infusion as well as other antihypertensive, like nifedipine, captopril, etc., have also been used. Studies have also used nitroprusside and nitroglycerine to reduce after load. All patients must receive antitetanus prophylaxis. The clinical scoring and treatment in scorpion sting is given in Table 4.

SPIDER BITE

Three main syndromes result from spider bite envenoming: (i) latrodectism, (ii) loxoscelism and (iii) funnel-web spider envenoming. Latrodectism is related to neurotoxins present in the venom of widow spiders. Most cases present with headache, lethargy, irritability, myalgia, tremor, fasciculation, or ataxia. Loxoscelism is caused by envenoming by spiders of the family sicariidae. It may present with a stroke due to a severe coagulopathy. The venom of funnel-web spiders also has neurotoxins that stimulate

by mansdocs.com

Table 4: Clinical score of scorpion envenoming and corresponding treatment.

Grade I	• Local pain (sometime associated with local paresthesia, erythema, ecchymosis, blisters)	Analgesics
Grade II	• *Mild systemic envenoming*: Idem grade I + hyperthermia + Cardiovascular and respiratory symptoms: tachycardia, arrhythmia, dyspnea, hypertension/hypotension, electrocardiographic abnormalities, priapism • Hypersecretory syndrome (salivation, sweating, bronchorrhea, nausea, vomiting, diarrhea, urination) • *Digestive tract*: Abdominal distension, abdominal cramps • *Neuromuscular disorders*: Dysfunction of either skeletal or cranial muscles, confusion, agitation, fasciculation, dystonia, vision disorders, ptosis, aberrant eye movements • *Biological disorders*: Hyperleucocytosis, hyperglycemia, acidosis	Idem + • Immunotherapy: Dose depending on antivenom titer • Prazosin 30 µg/kg orally every 6 hours • Midazolam 0.05–0.2 mg/kg orally or IV (or diazepam 0.5 mg/kg IV or rectally) every 12 hours
Grade III	• *Life-threatening envenoming*: Idem grade II + multivisceral failure • *Cardiovascular symptoms*: Heart failure, cardiogenic shock, pulmonary edema • Diaphoresis • *Neuromuscular disorders:* Dysfunction of both skeletal and cranial muscles, convulsions, paralysis, Glasgow score less than 6 (in absence of sedation) • *Biological disorders*: SaO_2, 90%, increasing biomarkers of cellular necrosis, electrolytic anomalies (decrease of Na+ and Ca++, increase of K+)	Idem + • Transfer to ICU

neurotransmitter release, resulting in sensory disturbances and muscle paralysis. Proper management of the envenomed patient, including prompt transport to the hospital, correction of the hemostatic disorder, ventilatory support and administration of antivenom, significantly reduces the risk of neurological complications which, in turn reduce the mortality and improve the functional outcome of survivors.

Clinical Features

Clinical Features include muscle spasm, localized diaphoresis, piloerection and hypertension. Bites usually occur on an extremity and may or may not be accompanied by a stinging sensation. A period of 10–60 minutes may pass before other symptoms develop. Shoulder, back, chest and abdominal pain often develop as the venom effect moves proximal to the bite site. There may be a marked feeling of restlessness, but intractable pain is the major complaint of Latrodectus-envenomated patients. The majority of symptoms peak during the first 48 hours after envenomation and decline within 2–3 days. Symptoms may persist up to 7 days; however, generalized weakness, muscle pain and malaise may last for weeks.

Treatment

Parenteral opioids and antivenom are most successful in treating the signs and symptoms of severe envenomation. Antivenin is very effective at relieving acute pain and resolving systemic symptoms, and its administration up to 90 hours post-envenomation has been associated with clinical resolution of symptoms. Current recommendations for when to give antivenin include grades 2 or 3 envenomation, envenomation refractory to opiates and sedative hypnotics, patients suffering from rare effects such as priapism, and pregnant patients at risk for miscarriage due to latrodectism-related muscle cramping and hypertension.

INSECT BITE

Insect sting of order Hymenoptere (which comprises wasps and bees) is a relatively common insect assault of common incidence in villages and forest pockets affecting mainly farmers, gardeners and farm animals. However, it has been estimated that every year a large number of people died due to massive sting envenomation, particularly in Southeast Asia. The pathogenic mechanisms responsible for the clinical sequel following insect stings include allergic reactions, rhabdomyolysis, hemolysis and direct tissue toxicity. Pharmacologically, venom in sting is a pool of active peptides mixed with certain inorganic elements and acids; venom contains active amines (serotonin and histamine), kinins and histamine-releasing peptides (mastoparans). They are the cause of toxic systemic reactions. The venom acts primarily at cellular level, breaks membrane barriers, damages organ system and deteriorates the biochemical regulation of body.

by mansdocs.com

Box 1: Signs and symptoms of severe insect stinging.

- Difficulty in breathing
- Hives that appear as a red, itchy rash and spread to areas beyond the sting
- Swelling of the face, throat or mouth tissue
- Wheezing or difficulty in swallowing
- Restlessness and anxiety
- Tachycardia
- Dizziness
- Hypotension

Box 2: Indications for ICU referrals.

- Circulatory shock, cardiac dysfunction, pulmonary edema
- Hemorrhage, hypovolemia
- Coagulopathy, disseminated intravascular coagulation (DIC)
- Coma, seizures, intracranial hemorrhage
- Cranial nerve dysfunction
- Rhabdomyolysis, renal failure, hyperkalemia
- Gastrointestinal bleeding
- Respiratory failure
- Anaphylaxis (to component of venom or antivenom)

The severity of an insect sting reaction varies from person to person. There are three types of reactions as as: (i) local swelling and irritation, (ii) generalized anaphylactic responses and (iii) serum sickness like symptoms which include hemolysis, disseminated intravascular coagulation, rhabdomyolysis and ARF. A single sting can cause IgE-mediated anaphylaxis; however, mass stings can cause systemic reactions of toxin-mediated cellular damage. Although severe allergic reactions are not that common, they can lead to shock, cardiac arrest and unconsciousness. This type of reaction can occur within minutes after a sting and can be fatal (Box 1).

Treatment

Epinephrine and steroids should be advised in case of anaphylaxis, but in case of toxin-related multisystem injury, hemolysis and rhabdomyolysis are the two major factors that cause acute renal failure. Optimal hydration is also indispensable to avoid renal damage caused by rhabdomyolysis in addition to those reagents. Patients may require hemodialysis.

ICU referrals in fatal envenomation are listed in Box 2.

BIBLIOGRAPHY

1. Bawaskar HS, Bawaskar PH. Utility of scorpion antivenin vs prazosin in the management of severe Mesobuthus tamulus (Indian red scorpion) envenoming at rural setting. J Assoc Physicians India. 2007;55:14-21.
2. Bawaskar HS, Bawaskar PH. Scorpion envenoming and the cardiovascular system. Trop Doct. 1997;27(1):6-9.
3. Brutto OHD. Neurological effects of venomous bites and stings: snakes, spiders, and scorpions. Handb Clin Neurol. 2013;114:349-68.
4. Cheng D, Dallaro JA, Yakubi R. Scorpion envenomation. eMedicine. 2009.
5. Chippaux JP. Emerging options for the management of scorpion stings. Drug Des Devel Ther. 2012;6:165-73.
6. Chugh KS. Snake bite induced acute renal failure in India. Kidney International. 1989;35:891-907.
7. Deshpande PR, Farooq AKK, Bairy M, et al. Acute renal failure and/or rhabdomyolysis due to multiple bee stings: a retrospective study. N Am J Med Sci. 2013;5(3):235-9.
8. Iyaniwura TT. Snake venom constituents: biochemistry and toxicology (parts 2). Vet Hum Toxical. 1991;33(5):475-80.
9. K Ito, Imafuku S, Nakayama J. Rhabdomyolysis due to multiple wasp stings, Case Reports in Dermatological Medicine. 2012;2012.doi:10.1155/2012/486724.
10. Murphy CM, Hong JJ, Beuhler MC. Anaphylaxis with Latrodectus antivenin resulting in cardiac arrest. J Med Toxicol. 2011;7(4):317-21.
11. Murthy KRK, Zare MA. Scorpion anti venom reverses metabolic, electrocardiographic, and hormonal disturbances caused by the Indian red scorpion Mesobuthus tumulus concanesis, pocock envenomation. J Venom Anim Toxins. 2002;8(1).
12. National snakebite management protocol, India. (2008). [online] Available from www://mohfw.nic.in (Directorate General of Health and Family Welfare, Ministry of Health and Family Welfare, India).
13. Rachaiah NM, Jayappagowda LA, Siddabyrappa HB, et al. Unusual case of acute renal failure following multiple wasp stings. N Am J Med Sci. 2012;4(2):104-6.
14. Ramachandran LK, Agarwal OP, Achyutan KE, et al. Fractionation and biological activities of venoms of the Indian scorpions Buthus tamulus and Heterometrus bengalensis. Indian J Biochem Biophys. 1986;23(6):355-8.
15. Tun P, Khin Aung Cho. Amount of venom injected by Russell's Viper (Vipera russelli). Toxicon. 1986;24(7):730-3.
16. Warrell D, Guidelines for the clinical management of snake bites in the South-East Asia region. Southeast Asia, Delhi: Regional office of WHO; 2005.

by mansdocs.com

CHAPTER

68

Care of Obese Patient in ICU

Gaurav Kochhar, Abhinav Gupta

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2).

DEFINITION AND CLASSIFICATION OF OBESITY

The World Health Organization (WHO) defines overweight as BMI greater than or equal to 25 and obesity as BMI greater than or equal to 30.

Extent of Problem

According to WHO global estimates from 2008, overall more than 10% of the world's adult population were obese. In India overall percentage of people who were found to be overweight/obese in 2007 national family health survey data was 12.1% of males and 16% of females. The percentage was found to be much higher in certain states (Punjab 30.3% males and 37.5% females, Kerala 24.3% males and 34% females).

At least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of the ischemic heart disease burden are attributable to overweight and obesity. The systemic alterations and co-morbidities associated with obesity are listed in Table 1.

Table 1: Systemwise overview of physiological alterations and associated complications/comorbidities of obesity.

Cardiovascular	*Respiratory*	*Gastrointestinal*	*Endocrine/metabolic*
Physiological alterations	Physiological alterations	Physiological alterations	• Increased amount of lean body mass
• ↑Central venous pressure: increased by high intra-abdominal and pleural pressures	• ↑Upper airway resistance	• Intra-abdominal pressure: ↓pH and increase gastric volume: GERD and aspiration risk	• Increased resting energy expenditure
• ↑blood volume and polycythemia	• ↓Total lung capacity, ↓Vital capacity, ↓Functional residual capacity	• Complications & associated morbidity	• Accelerated protein degradation
• ↑cardiac output and ventricular work	• ↓Respiratory system compliance	• Aspiration	• Exacerbation of stress-induced hyperglycemia

Contd...

by mansdocs.com

Contd...

Cardiovascular	*Respiratory*	*Gastrointestinal*	*Endocrine/metabolic*
• Complications and associated morbidity	• ↑Pulmonary artery occlusion pressure	• GERD	• Adipose tissue releases a large number of bioactive mediators that can result in abnormal lipids, insulin resistance, inflammation, and coagulopathies.
• Congestive heart failure	• ↓Hypercapnic ventilatory response: contributes to obesity hypoventilation syndrome	• Abdominal compartment syndrome	• Complications and associated morbidity
• Hypertension	Complications and associated morbidity	• Nonalcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH)	• Diabetes mellitus (type II)
• Myocardial infarction	• Difficult airway	• Gastroparesis	• Metabolic syndrome/syndrome X
• Dyslipidemia	• Hypoventilation (Pickwickian) syndrome	• Gallstones and biliary tract disease	• Hypothyroidism
	• Obstructive sleep apnea		
	• Difficult weaning		
	• Respiratory failure		
Neurologic/psychologic	*Hematologic*	*Pharmacology*	*Mechanical problem*
Physiological alterations	Physiological alterations	Complications and associated morbidity	Complications and associated morbidity
• ↑Intracranial pressure: associated with raised intra-abdominal and pleural pressures	• Hypercoagulable, platelet hyperactivity: increased risk of VTE	Altered pharmacokinetics	• Difficult IV access
Complications and associated morbidity	• Impaired fibrinolysis and elevated fibrinogen.		• Requires special monitoring standard cuff may overestimate both systolic and diastolic blood pressures
• Stroke	Complications and associated morbidity		• Pressure area cares
• Depression	• Deep vein thrombosis and pulmonary embolus (VTE)		• More staff and equipment required to move
• Idiopathic intracranial hypertension	• Hypercoagulable state		• Imaging difficulties (difficult to ultrasound, may not fit in CT or MRI scanners)
• Disordered eating	• Chronic venous stasis		

(VTE: Venous thromboembolism; GERD: Gastroesophageal reflux).

Airway

Obesity poses definite challenge in terms of airway control, ventilation and more rapid desaturation (Fig. 1), giving lesser margin of safety. In one study difficult intubation rate was 15.5% in obese patients versus 2.2% in lean patients.[1] Both anatomical as well as physiological alteration contribute to this difficulty.

However, contrary to expectation, BMI alone does not predict difficult airway in obese patients. Neck circumference has been identified as the single best predictor of problematic intubation in morbidly obese patients. A larger neck circumference is also associated with a higher Mallampati score, grade 3 views at laryngoscopy, and obstructive sleep apnea.

It should be noted that life-threatening cases in morbidly obese airway management result not from failure to intubate but from failure to ventilate. One should anticipate difficult airway and ventilation and be ready to tackle it (Table 2). Some of the anticipatory measures which should be taken are availability of short-handled "stubby" laryngoscope, ramp positioning of patients with elevation of chest and head with the goal of elevating the ears to the level of the sternal notch.

by mansdocs.com

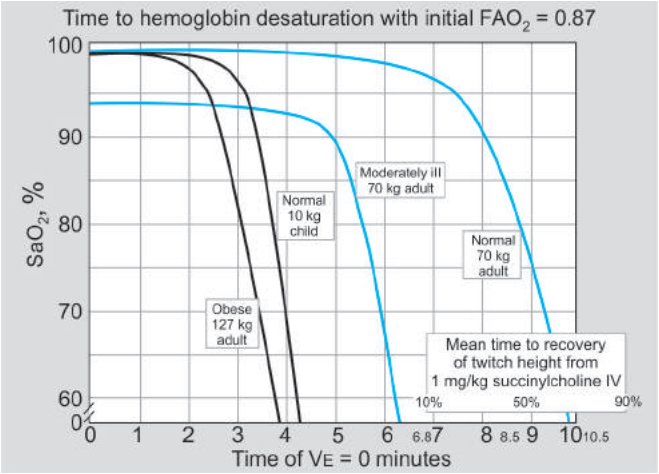


Fig. 1: SaO_2 versus time of apnea for various types of patients.[19] (SaO_2: Arterial oxygen saturation).

Table 3: BMI and the associated risk.

Classification	*BMI (kg/m²)*	*Risk of developing health problems*
Underweight	<18.5	Increased
Normal weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obese		
Class 1	30.0–34.9	High
Class 2	35.0–39.9	Very high
Class 3	40.0–49.9	Extremely high
Superobese	≥50	Exceedingly high

Table 2: Factors contributing to difficulty in airway management.

Anatomical	*Physiological*
• Increased tongue size, increased facial girth, smaller pharyngeal area • Redundant pharyngeal tissue • Small space between mandible and sternal pad of fat • Increased neck circumference • Limited atlanto-occipital joint mobility • Restricted neck movement • Increased breast size • Increased chest girth • Increased abdominal girth	Limited pulmonary reserve due to • Cephalad displacement of diaphragm • Reduction in expiratory reserve volume (ERV is the most sensitive indicator of the effect of obesity on pulmonary function) • Reduced functional residual capacity (FRC), total lung capacity (TLC) • Decreased chest wall compliance and restrictive pattern on pulmonary function testing (PFT) • V/Q mismatch • Rapid desaturation as compared to nonobese patients (Fig. 1)

Mechanical Ventilation

Alteration of physiology and ventilatory mechanics (Table 3) mandates modification in ventilation strategy. Initial settings of tidal volume (Vt) should be based on ideal body weight (IBW) not total body weight (TBW) to avoid alveolar overdistension and barotraumas and it should be further adjusted according to desired plateau pressure and arterial blood gases (ABGs).

Male IBW = 50 kg + 2.3 kg per inch of height over 5 feet

Female IBW = 45.5 kg + 2.3 kg per inch height over 5 feet

Positioning the patient in reverse Trendelenburg may decrease intrathoracic pressure, unload diaphragm, prevent atelectasis, decrease V/Q mismatch and hypoxemia.

Application of positive end-expiratory pressure (PEEP) prevents atelectasis, promotes recruitment and has been shown to improve respiratory function in obese but not in normal subjects during anesthesia and paralysis.[2]

Similarly, noninvasive ventilation has been shown to have benefit during weaning of obese patient. In one such study involving 62 morbidly obese patients in MICU, 16% absolute risk reduction in respiratory failure was seen when noninvasive ventilation (NIV) was instituted immediately post-extubation.[3]

Pharmacokinetics

In obese patients there is a change in body composition, activity of P450 enzymes, volume of blood, besides risk of miscalculation of glomerular filtration rate (GFR) by conventional method. All these factors need to be considered while deciding dosages.

Adipose tissue has 25-50% water content and it cannot be generalized that, in an obese patient all lipophillic drugs will have greater increase in volume of distribution (Vd) and hydrophilic drugs will have only minimal alteration in volume of distribution.

by mansdocs.com

Creatinine clearance equations have been shown to be inaccurate in obesity. TBW overestimates creatinine clearance and IBW underestimates creatinine clearance rate when Cockcroft-Gault GFR equation is used. Modifications of Diet in Renal Disease (MDRD) equation has been shown to predict GFR fairly accurately in obese patients.
MDRD equation:

GFR (expressed in mL/min/1.73 m^2) = 170 × [plasma creatinine]$^{-0.999}$ × [age]$^{-0.176}$ × [0.762 if patient is female] × [1.180 if patient is African American] × [SUN]$^{-0.170}$ × [albumin]$^{+0.318}$

Certain general pharmacokinetic principle which can help in dose adjustment in obesity are mentioned below:

In case of drugs having a smaller Vd that approximates blood volume, IBW should be used.

With drugs having a large Vd (>0.7 L/kg), an adjusted weight or actual weight should be used.

AW = IBW + 0.4 (TBW - IBW)

For drugs with narrow therapeutic index and dosing as per weight, IBW should be used.

Weight-based drugs should be titrated to desired effects.

Clinical end points, therapeutic serum levels and signs and symptoms of drug toxicity should be monitored.

Opinion of critical care pharmacologist, if available, should be taken.

Hematology

Morbid obesity is a major independent risk factor for deep venous thrombosis and sudden death from acute postoperative pulmonary embolism (PE).

Obesity is associated with increased viscosity, fibrinogen level, plasminogen activator inhibitor (adipocytes produce PAI-1), decreased capacity of endothelium to secrete tissue plasminogen activator (tPA) and decreased fibrinolysis creating a hypercoagulable state.

American Society of Breast Surgeons (ASBS) has reported that more than 48% surgeons have lost at least one patient to fatal PE. Moreover, association of obesity with poor respiratory reserve and pulmonary hypertension may make such patient less tolerant to PE.

A study done to evaluate the use of thromboprophylaxis guidelines[4] showed that obesity is one of the more common risk factors among patients with preventable venous thromboembolism (VTE). Low-molecular-weight heparins are currently popular for thromboembolism prophylaxis.

For thromboprophylaxis in obese patients undergoing surgery, the minimal evidence suggests that weight-based prophylactic dosing is preferable to fixed dosing.[5–8]

Factor Xa activity is inhibited appropriately when the drug is administered to obese patients in doses based on TBW up to 144 kg (enoxaparin), 165 kg (tinzaparin) and 190 kg (dalteparin). There may be some benefit in extending the postsurgical treatment to up to 3 weeks.

However, in case of PE in post bariatric surgery patient, pharmacologic thrombolytic therapy should be avoided for 10–15 days postoperatively.

Nutrition

- Obese patients have increased amount of lean body mass and have increased resting energy expenditure, secondary to increased BMI. In the setting of critical illness, energy stores from lean mass is used preferentially in the obese unlike lean people who use free fatty acid (FFA) leading to accelerated protein degradation. In addition, obese are likely to have exacerbation of stress-induced hyperglycemia.
- Indirect calorimetry is the preferred method for measuring resting energy expenditure (REE) but this is often unavailable or impractical. Although, there is no consensus as to which prediction for REE is most accurate in obese patients, the Penn State equation and adjusted Harris-Benedict Equation (HBE) have the strongest evidence to support their use.
- In general, high protein hypocaloric feeding is preferred for critically ill obese patients (supported by SCCM/ASPEN joint consensus statement). This is believed to avoid complications of overfeeding such as hyperglycemia, fluid retention, increased lipogenesis, hepatic steatosis, increased CO_2 production and also helps to preserve fat free mass (FFM) and promote steady weight loss.
- Enteral feeding is preferred. Aim is to provide 60–70% of target energy requirements or 11–14 kcal/kg actual body weight per day with proteins contributing 50–60% total calories, i.e.
  - 2.0 g/kg IBW proteins per day for class I and class II obesity (BMI 30–35 and 35–40 respectively)
  - 2.5 g/kg IBW proteins per day for class III obesity (BMI > 40)
- However, high protein hypocaloric enteral feeding approach has not been validated by a high quality randomized controlled trial (RCT). Another concern is that mild obesity may confer a survival advantage in critical illness; steady weight loss through hypocaloric feeding might negate this.

by mansdocs.com

OBESITY PARADOX

Recent studies suggest that obese patients (BMI > 30) with critical illness have equivalent or lower mortality rates than equally sick, nonobese patients.[9-17] These observations are supported by a meta-analysis which suggested that patients with a BMI more than 40 had decreased hospital mortality compared to normal weight patients, although this did not reach statistical significance [relative risk (RR) 0.83, 95% confidence interval (CI) 0.66-1.04].[16]

Because we intuitively might expect a mortality increase in the obese population, this phenomenon has been coined as "obesity paradox". But morbidly obese patients have longer hospital stays.

Reasons for the lack of mortality increase in extremely obese patients are unknown. However, a recent study found that obese patients with acute lung injury have lower levels of several proinflammatory cytokines (interleukin-6, interleukin-8 and surfactant protein D),[18] raising the possibility that obese may develop a reduced inflammatory response in critical illness. Another hypothesis is that increased energy stores and increased lean body mass in obese patients may provide protective effects.

CONCLUSION

Obesity mandates special care in ICU with following points to be kept in mind:

- Anticipation of difficulty in airway management and taking proper precautions
- Modified approach to mechanical ventilation with proven benefit of PEEP and NIV
- Risk of cardiovascular (CVS) complications, unreliable noninvasive blood pressure (BP) monitoring and therefore need for invasive monitoring
- There is increased risk of venous thromboembolism thromboprophylaxis, and possible benefit of using weight-based heparin dosing
- Modification of diet
- Anticipation of mechanical and logistic challenges.

REFERENCES

1. Juvin P, Lavaut E, Dupont H, et al. Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg. 2003;97(2):595-600.
2. Pelosi P, Ravagnan I, Giurati G, et al. Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. Anesthesiology. 1999;91(5):1221-31.
3. El-Solh AA, Aquilina A, Pineda L, et al. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J. 2006;28(3):588-95.
4. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest. 2001;120(6):1964-71.
5. Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther. 2002;72(3):308-18.
6. Wilson SJ, Wilbur K, Burton E, et al. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. Haemostasis. 2001;31(1):42-8.
7. Al-Yaseen E, Wells PS, Anderson J, et al. The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. J Thromb Haemost. 2005;3(1):100-2.
8. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. Thromb Res. 2005;116(1):41-50.
9. Aldawood A, Arabi Y, Dabbagh O. Association of obesity with increased mortality in the critically ill patient. Anaesth Intensive Care. 2006;34(5):629-33.
10. Ray DE, Matchett SC, Baker K, et al. The effect of body mass index on patient outcomes in a medical ICU. Chest. 2005;127(6):2125-31.
11. Sakr Y, Madl C, Filipescu D, et al. Obesity is associated with increased morbidity but not mortality in critically ill patients. Intensive Care Med. 2008;34(11):1999-2009.
12. O'Brien JM Jr, Phillips GS, Ali NA, et al. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. Crit Care Med. 2006;34(3):738-44.
13. Frat JP, Gissot V, Ragot S, et al. Impact of obesity in mechanically ventilated patients: a prospective study. Intensive Care Med. 2008;34(11):1991-8.
14. Garrouste-Orgeas M, Troché G, Azoulay E, et al. Body mass index. An additional prognostic factor in ICU patients. Intensive Care Med. 2004;30(3):437-43.
15. Memtsoudis SG, Bombardieri AM, Ma Y, et al. Mortality of patients with respiratory insufficiency and adult respiratory distress syndrome after surgery: the obesity paradox. J Intensive Care Med. 2012;27(5):306-11.
16. Hogue CW Jr, Stearns JD, Colantuoni E, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. Intensive Care Med. 2009;35(7):1152-70.
17. Martino JL, Stapleton RD, Wang M, et al. Extreme obesity and outcomes in critically ill patients. Chest. 2011;140(5):1198-206.
18. Stapleton RD, Dixon AE, Parsons PE, et al. The association between BMI and plasma cytokine levels in patients with acute lung injury. Chest. 2010;138(3):568-77.
19. Benumof JL, Dagg R, Benumof R. Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology. 1997;87(4):979–82.

by mansdocs.com

CHAPTER

69

Imaging in Intensive Care Unit

Chander Mohan, Rajul Rastogi

INTRODUCTION

As patients in intensive care units (ICU) are critically ill, imaging of these patients within the ICU premises represents a specialized and technically challenging environment. The ICU patients are often unconscious and almost always connected to life-supporting or monitoring equipment. Consequent to this, majority of the diagnostic procedures are performed with limited cooperation from the patient, and ultimate imaging quality compromises. Thus, this technically challenging situation demands special expertise of the technicians and radiologist. In this chapter, we will be discussing the role of diagnostic imaging and imaging procedures in critically ill patients while in ICU.

Chest Imaging

Imaging of the chest in critically ill patients within ICU is limited to various types of chest radiographs and ultrasonography.

Role of Radiograph

Critically ill patients in ICU frequently undergo chest radiography for multiple reasons making it the commonest diagnostic investigation in this setting. Radiography is done by portable x-ray machines with digital platform to allow faster processing, better quality, and teleradiology if the need arises. Following may be the indications for the same:

- Baseline radiograph when the patient is shifted to ICU. Besides the basic pleuropulmonary and cardiac status, it helps us in knowing the pulmonary volume status before and after the assisted ventilation
- Diagnosis of various respiratory/cardiac conditions in symptomatic conditions
- Diagnosis of coexisting respiratory/cardiac conditions in patients suffering from other diseases
- Differentiating cardiogenic and non-cardiogenic edema in the limbs/body
- Studying the progression/regression of the respiratory/cardiac diseases
- Monitoring pleuropulmonary/cardiopulmonary status following invasive procedures
- To monitor the optimal placement of variety of invasive devices and related complications in the thoracic cavity. It is mandatory to order a chest radiograph following placement of indwelling catheters, tubes or other devices in the chest because nearly all of these devices carry the risk of improper positioning (approximate incidence of 10–15%), coiling, knotting or fracture, leading at times to life-threatening complications especially in patients with little cardiopulmonary reserve. The commonly placed devices and their normal position may be listed as below:
  - *Nasogastric tube*: Its distal tip should ideally be positioned in the gastric antrum. Presence of distal tip within esophagus increases the risk of aspiration. Malposition of nasogastric tube in trachea/bronchus and pharyngeal/esophageal perforation are the associated complications.
  - *Endotracheal intubation*: The distal tip of this tube should ideally be midway between the larynx and

by mansdocs.com

carina, corresponding approximately to a position 5–7 cm above the carina in neutral neck position that crudely corresponds to the level of medial ends of both clavicles. Flexion and extension of the neck can displace the tube tip 2–4 cm in either direction. Malposition may include inadvertent selective intubation of bronchus leading to hyperinflation of ipsilateral lung, ipsilateral pneumothorax due to higher ipsilateral pulmonary pressure or contralateral lung collapse. Inadvertent esophageal placement of endotracheal tube may lead to air-fluid level adjacent to trachea/overdistended stomach/duodenum with respiratory compromise. Overinflation of tube cuff is indicated by the focal increase in tracheal diameter that may lead to tracheal mucosal ischemia (Figs. 1 to 4).

- *Tracheostomy tube*: Distal tip of this tube should be at the recommended level of D3 vertebral body, filling less than two-thirds of the tracheal lumen without obvious tracheal distension. Potential complications include subcutaneous emphysema, pneumomediastinum, pneumopericardium and rarely mediastinal hemorrhage, leading to superior mediastinal widening on chest radiograph (Fig. 5).
- *Intercostal drain tube*: This tube is normally inserted through the fourth intercostal space in anterior or midaxillary line with its tip directed anterosuperiorly in cases of pneumothorax and posteroinferiorly in cases of pleural effusion. The tip of this tube should not lie outside the chest. Malposition of intercostal drain tube (ICD) may occur with its tip in the pulmonary fissure or parenchyma. Accurate determination of ICD position requires lateral view in addition to frontal radiographs (Fig. 6).
- *Mediastinal drain tube*: This tube is similar in appearance to ICD except for its position. This tube is inserted following sternotomy.
- *Central venous line*: This line is inserted through the major veins of the body, usually subclavian, internal jugular or femoral veins into the superior vena cava (SVC). The tip of this central venous line should be distal to the last venous valve which is located at the junction of subclavian and internal jugular veins corresponding to a position medial to the inner border of first ribs on chest radiograph. The tip should be above the cavoatrial junction which corresponds to the inferior margin of the bronchus intermedius. Pneumothorax is a well-known complication of central venous line insertion especially in subclavian approach. Venous perforation is suggested by superior mediastinal widening, enlargement of cardiac shadow (due to



Fig. 1: Anteroposterior view of chest showing endotracheal and nasogastric tubes and left upper lobe consolidation in addition to pneumonitis in left lower lobe and bilateral minimal pleural effusion.

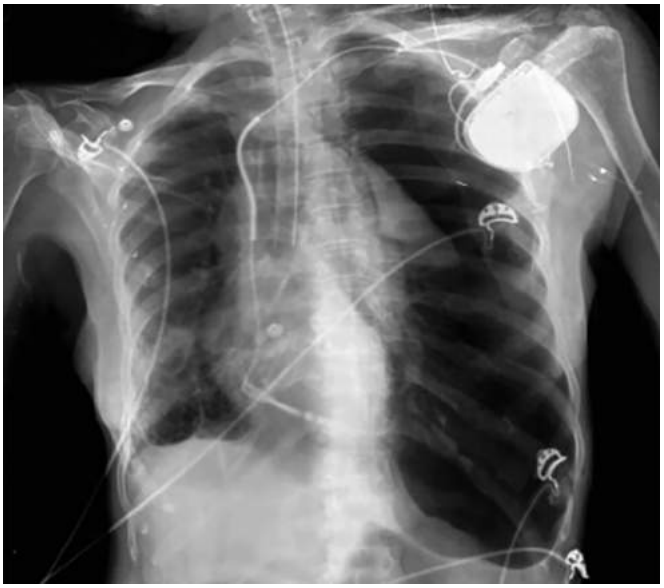


Fig. 2: Anteroposterior view of chest shows automated implantable cardioverter defibrillator, low-lying endotracheal tube and gross pneumothorax on left side causing complete collapse of left lung.

by mansdocs.com

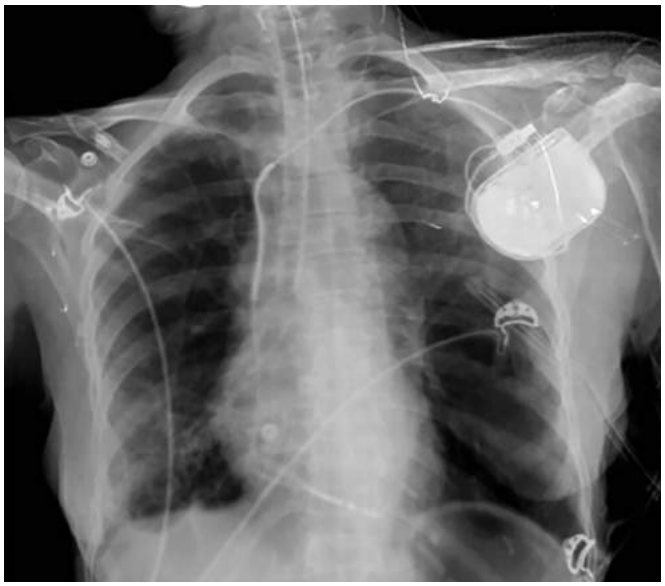


Fig. 3: Anteroposterior view of chest shows automated implantable cardioverter defibrillator, low-lying endotracheal tube and intercostal drain tube on left side with complete resolution of pneumothorax on left side causing complete collapse of left lung as seen in previous figure.

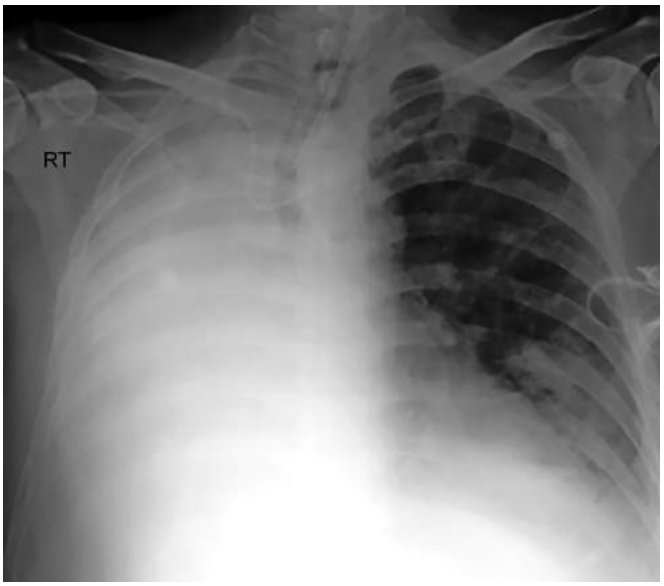


Fig. 4: Anteroposterior radiograph of chest shows complete collapse of right lung with mediastinal shift to right side.

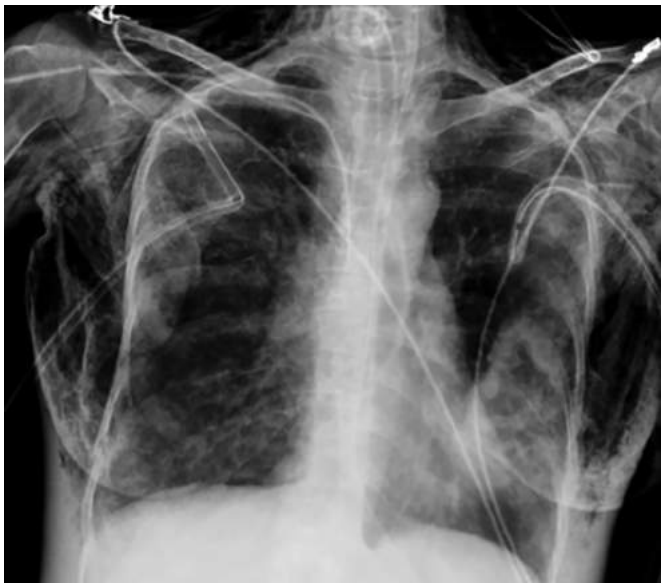


Fig. 5: Anteroposterior view of chest with tracheostomy and nasogastric tubes and bilateral intercostal drain tube in situ with massive subcutaneous emphysema.



Fig. 6: Posteroanterior view of chest showing pneumothorax on right side with malpositioned intercostal drain tube.

pericardial effusion), and appearance of new pleural effusion. Curving tip of the line laterally or along the lateral border of SVC may represent radiographic signs of impending perforation. Malposition may occur when the line enters one of the tributary of vein such as azygos vein or internal mammary vein. Inadvertent cannulation of carotid vessels is not uncommon (Figs. 7 to 9).

- *Pulmonary artery catheter or Swan-Ganz catheter*: This catheter is inserted through the antecubi-

by mansdocs.com



Fig. 7: Anteroposterior radiograph of chest in a neonate showing endotracheal and nasogastric tubes in situ.

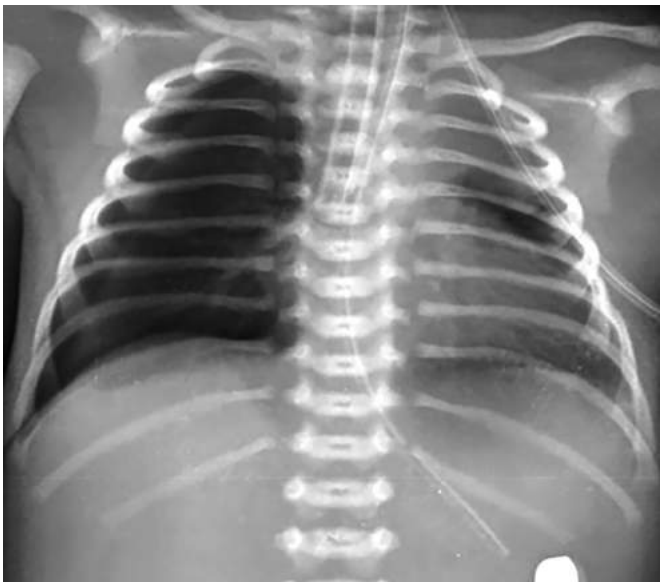


Fig. 8: Anteroposterior radiograph of chest in neonate with low-lying distal end of endotracheal tube and mild pneumothorax on right side.

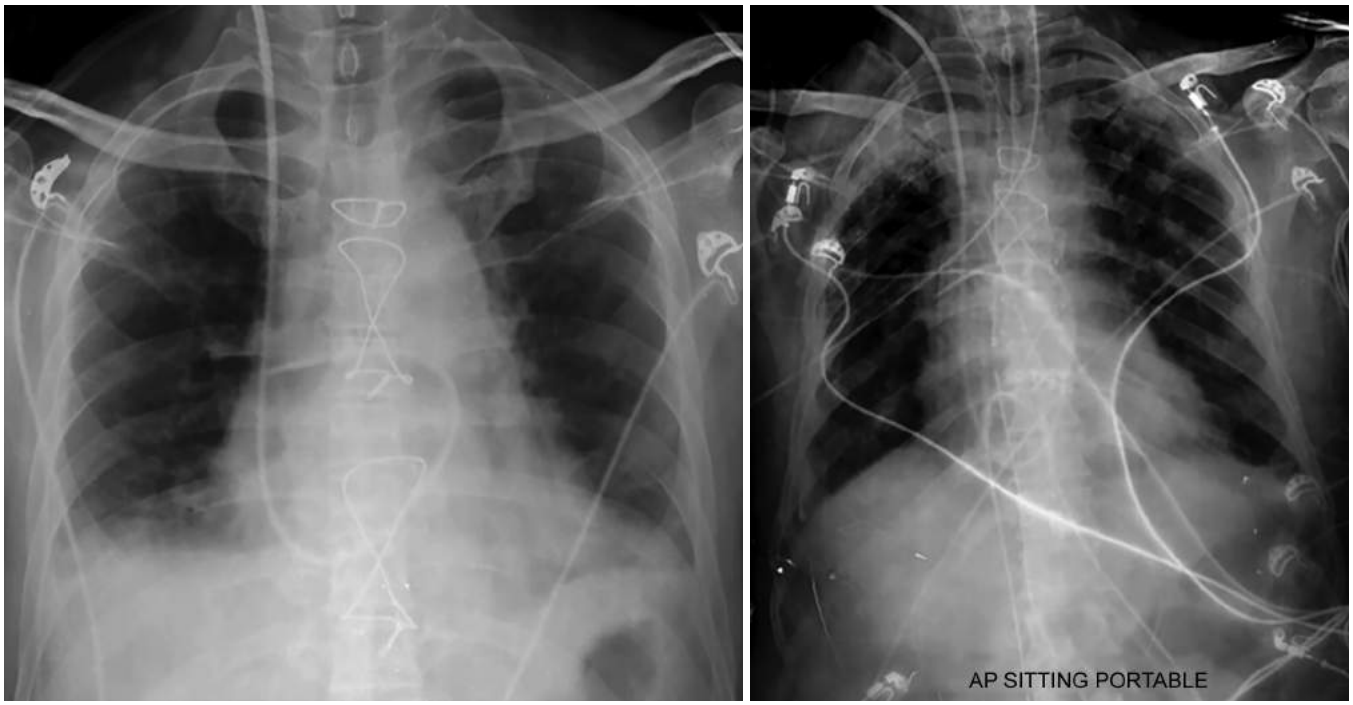


Fig. 9: Anteroposterior radiograph of chest showing curling of distal end of central venous line.

tal, jugular, subclavian or rarely through femoral veins into the right or left pulmonary artery with its tip not more than 1 cm from the mediastinal margin or crudely not beyond the pulmonary hilum. The common complications are pulmonary infarcts, hemorrhage, intracardiac knotting or inadvertent insertion into inferior vena cava (IVC).

- *Intra-aortic balloon pump*: This pump is radiolucent except for its terminal part which appears as

by mansdocs.com

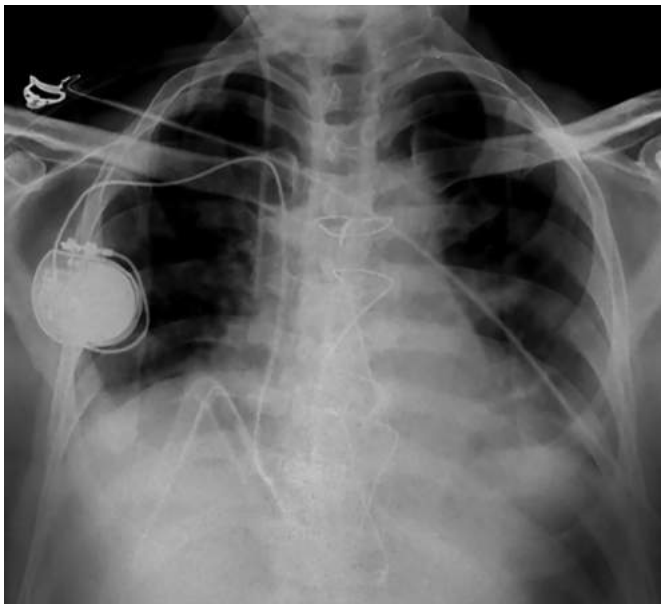


Fig. 10: Anteroposterior radiograph of the chest with single-lead pacemaker on right side.



Fig. 11: Anteroposterior view of chest showing automated implantable cardioverter defibrillator in situ.

3×4 mm^2 rectangular radiodensity, ideally located superior to the level of carina (second to third intercostal space). It is inserted through the femoral artery into the descending thoracic aorta.

- *Pacemaker*: This device consists of two units—a pulse generator (usually located in subcutaneous tissues at the level of second or third intercostal space) and lead wire containing electrodes. On chest radiograph, the tip of the lead wire is located in the right ventricular apex in single-lead type and in right atrium and right ventricular apex in double-lead type. An additional third lead is noted in the coronary sinus in three-lead type pacemaker. On frontal radiograph, the tip of right ventricular lead is directed inferiorly and laterally to the left side of midline (superior deviation may indicate entry into the coronary sinus), while on lateral chest radiograph the tip of right atrial lead is directed anteriorly (posterior deviation indicates entry into the coronary sinus). Besides malpositioning, common complications include intracardiac knotting, acute kinking, fracture and perforation of myocardium/vessels causing hemorrhage and subsequent enlargement of cardiac shadow (Fig. 10).
- *Automated implantable cardioverter defibrillator*: This device has a pulse generator and two leads—one each for right atrium and right ventricle. The leads are thicker than routine pacemaker leads with presence of characteristic radiodense bands with spring-coil appearance (Fig. 11).
- *Pediatric lines*: Umbilical vein catheter passes anteriorly in midline with posterior curve in the portal/hepatic area. On chest and abdominal radiograph, its distal tip is usually located at the level of D8/D9 vertebrae on right side of midline. Insertion of thin catheter may lead to transient air in the portal venous system. Malposition may occur in the hepatic or portal vein or at times into the left atrium through the patent foramen ovale. Coiling, bending or kinking of the catheter is undesirable.
- *Umbilical artery catheter* courses inferiorly into the iliac artery before turning superiorly to enter the aorta. It is seen posteriorly and to the left side of midline with its distal tip at the level of D6–D10 vertebral level. Sometimes, the inferior position of L3/L4 vertebra is preferred.
- *Sengstaken-Blakemore tube*: It is used for temporary control of bleeding esophageal varices with its distal bulb in gastric cardia and the proximal bulb in the distal esophagus. Inadvertent inflation of distal bulb in the distal esophagus may lead to esophageal perforation with subsequent pneumomediastinum, pneumothorax or subcutaneous emphysema.

by mansdocs.com

Systematic approach to the study of portable chest radiograph:

- Assess the technical quality of the radiograph
- Assess the location of invasive devices and common associated complications especially pneumothorax and mediastinal hematoma
- Assess the pulmonary volume and parenchymal appearance
- Evaluate the pleural spaces for effusions
- Assess the cardiopulmonary status



Fig. 12: Normal anteroposterior radiograph of chest in lying posture.

- Comparison should be done with the most recent previous radiograph.

Supine anteroposterior (AP) radiographs of chest show low pulmonary volumes, enlarged size of the heart, accentuated pulmonary vascular markings and widened superior mediastinum as a physiological variation. Hence, the diagnosis of congestive cardiac failure should be interpreted carefully (Figs. 12 to 15).

Role of Ultrasonography

Intensive care unit is ideal place for bedside portable ultrasonography. It is relatively inexpensive, easily available, portable, easily repeatable, reproducible, noninvasive, painless, safe and free of radiation. It requires a probe with footprint that fits easily into the intercostal space. Limitations of chest ultrasonography includes limited acoustic window secondary to surgical dressings and subcutaneous emphysema, and operator dependence.

Basic indications for ultrasonography:

- Evaluation of lung/thoracic cavity for early detection of life-threatening conditions as acute respiratory failure, acute circulatory failure
- Airway management in critically ill ICU patients (e.g. pre-intubation assessment, optimal intubation, double-lumen intubation, prognosis post-extubation, guiding percutaneous tracheostomy, etc.)
- Extended focused assessment with sonography for trauma (EFAST) for rapid identification of free fluid

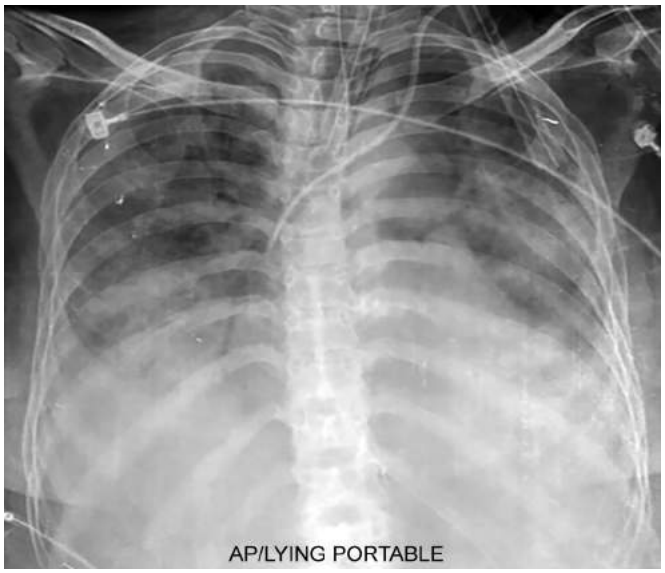


Fig. 13: Anteroposterior radiograph of chest in case of adult respiratory distress syndrome.



Fig. 14: Posteroanterior radiograph of chest shows sign of congestive cardiac failure.

by mansdocs.com

in the body cavities of the trauma patients who are hemodynamically unstable
- Achieving easy vascular access and a guide for regional analgesia
- Guiding insertion of the drain tubes in the chest for fluid collections.

Systematic approach in ultrasonography of chest:
- Indentify the echogenic horizontal line posterior to the rib line corresponding to the parietal pleura
- Indentify to-and-fro moving peripheral pulmonary margin posterior to pleural line as A-line corresponding to air/gas in the pulmonary parenchyma.

Pleural collections, peripheral pulmonary consolidation, interstitial syndrome and pneumothorax are easily identified by portable ultrasonography (Figs. 16 to 19).

The characteristic sign of pneumothorax on chest ultrasonography is the inability to distinguish pleural and lung interfaces. On M-mode, it gives rise to typical *stratosphere sign*. Absence of this sign does not rule out pneumothorax.

B-lines or comet tails refer to multiple echogenic linear foci beneath the pleural line and represent thickening of peripheral, interlobular, interstitial septae and hence may represent pulmonary edema.

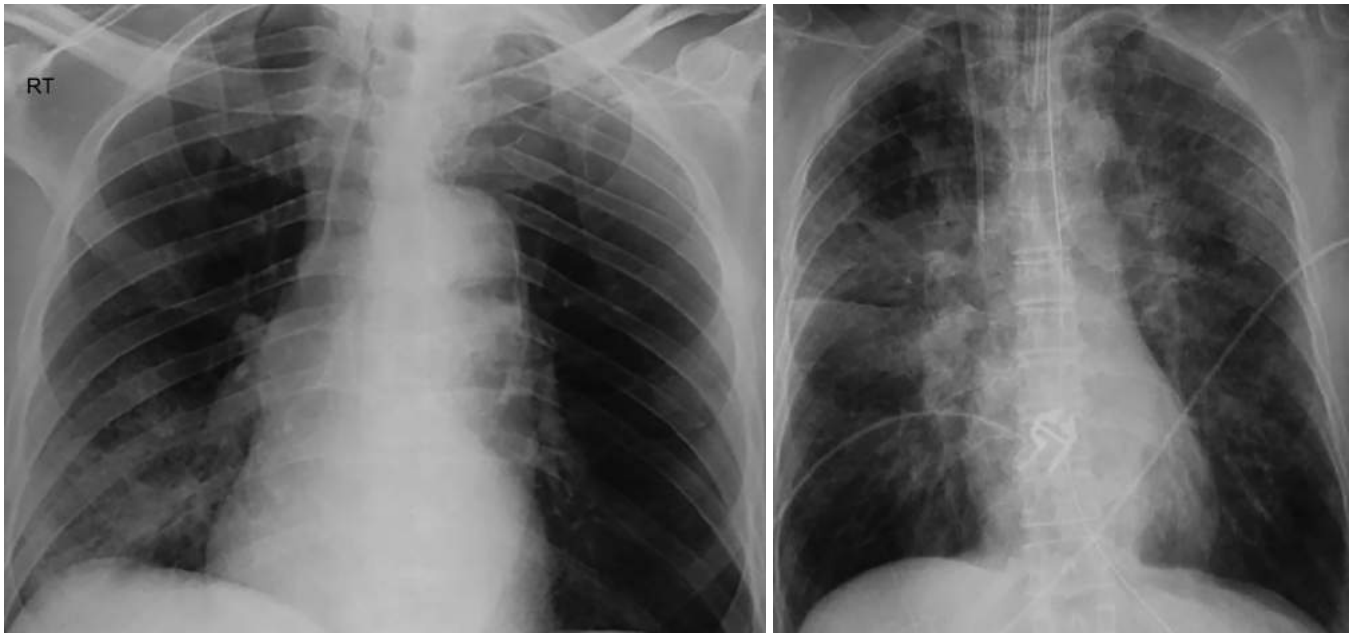


Fig. 15: Anteroposterior radiograph of chest in supine posture showing aspiration pneumonitis in two different cases.

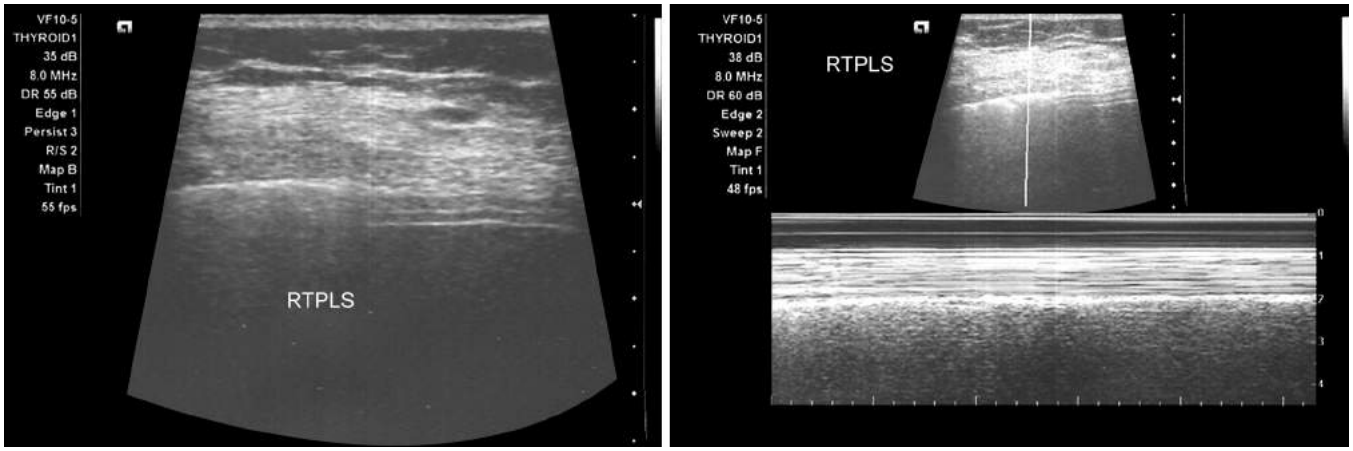


Fig. 16: Ultrasound scans of normal pleural space—B-mode (left) and M-mode (right).

by mansdocs.com

Sinusoid sign refers to the cyclical movement of the lung on inspiration and expiration as noted on M-mode in cases of pleural collections. A rough estimate of pleural fluid volume can be done by a simplified formula as *V = 20 × separating distance between visceral and parietal pleura in millimeter in end-expiratory phase*.

Translobar pneumonic consolidation shows liver-like echo pattern on ultrasonography (*tissue sign*), while in non-translobar pneumonic consolidation the separating line between normal and consolidated pulmonary parenchyma is irregular and hazy (*shred sign*).

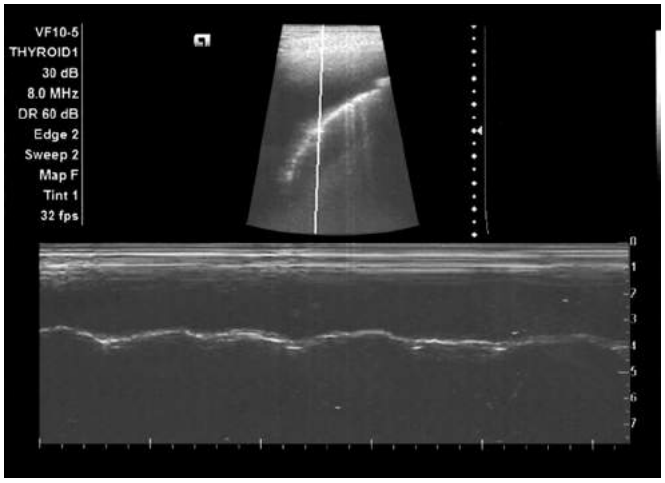


Fig. 17: Ultrasound scan in patient of pleural effusion.

Thickness of pretracheal soft tissues has been described as an indication of difficult airway intubation. The correct position of distal end of endotracheal tube can be easily confirmed by imaging it at the level of cricoid cartilage. Ultrasonography can act as a good guide for cricothyroidotomy in cases of can't intubate and can't ventilate scenario (CICV).

Ultrasonography has been used to lower the incidence of complication rates following percutaneous tracheostomy in many studies. Tracheostomy is normally done between second and third tracheal rings. Ultrasonography helps in assessing the intended area for tracheostomy in terms of vascular structures, depth of trachea, intercartilaginous space and determining the approximate width of the tracheal lumen for tube size especially in children.

Abdominal Imaging

Imaging of the abdomen in critically ill patients within ICU is limited to a few types of abdominal radiograph and ultrasonography.

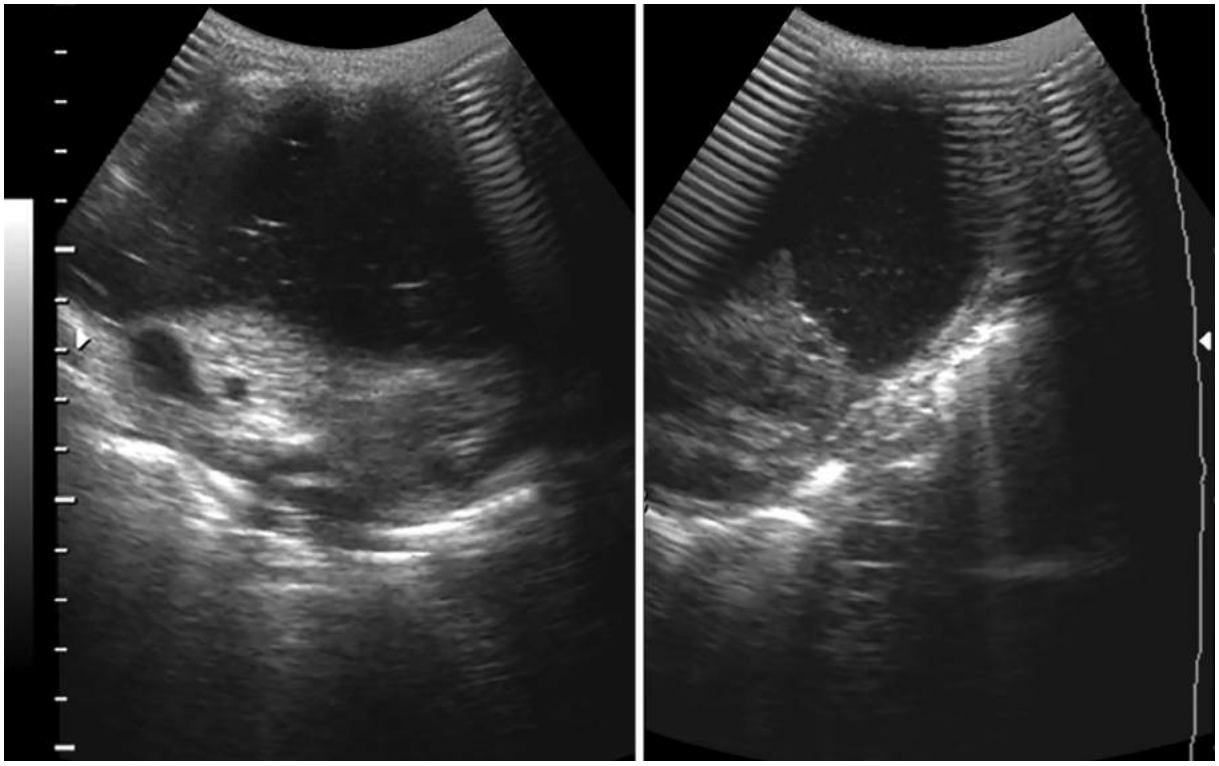


Fig. 18: Ultrasound scan in a patient of hemopneumothorax with tiny echogenic specks representing air bubbles.

by mansdocs.com

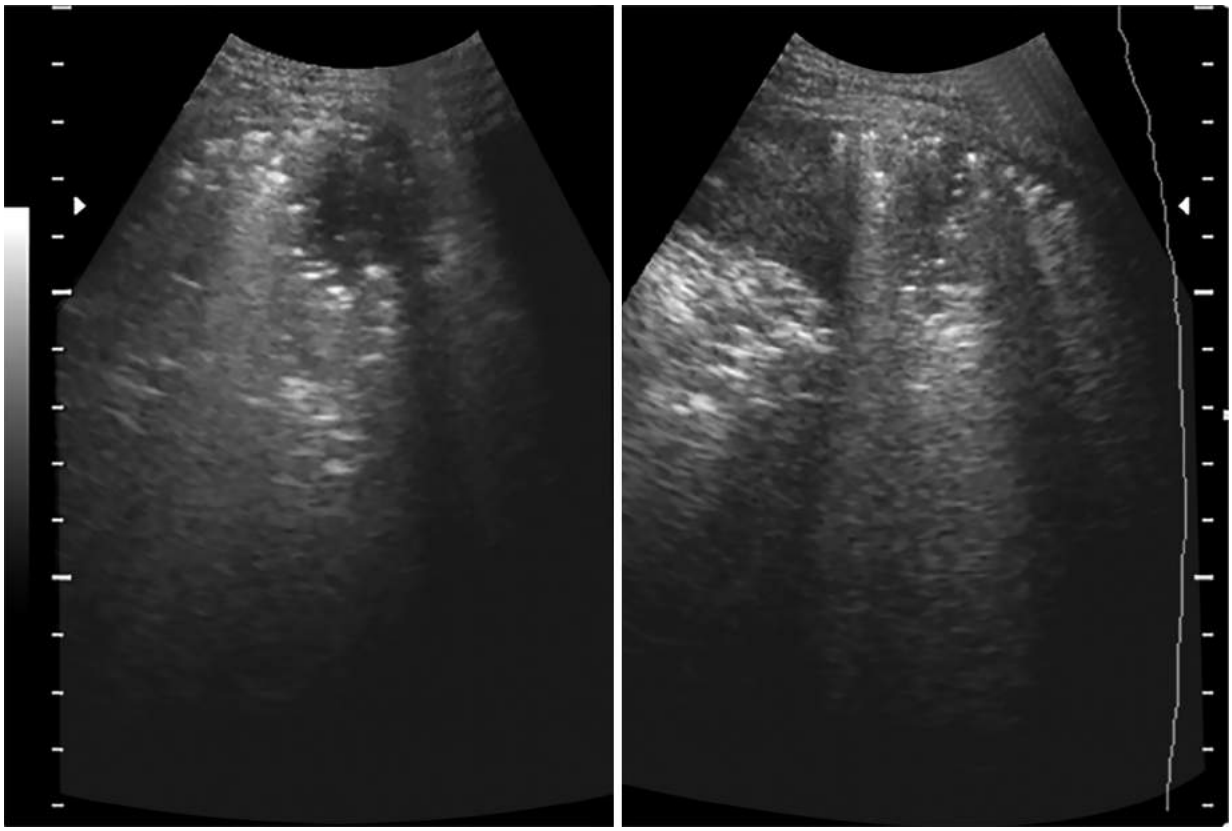


Fig. 19: Ultrasound scans show subsegmental pneumonic consolidation.

Most commonly advised radiograph of the abdomen in ICU settings is supine AP projection and sometimes sitting AP projection which helps us to differentiate the cause of abdominal distension as perforation or paralytic ileus (Figs. 20 to 22).

Certain signs that help us to diagnose free gas in the peritoneal cavity include:

- *Crescent sign* is seen as free subdiaphragmatic air on sitting posture.
- *Cupola sign* is seen as free midline air under central tendon of diaphragm as an inverted cup on supine radiograph.
- *Double-wall or Rigler's sign* refers to the presence of air on both sides of intestinal wall—lumen and peritoneal side of bowel.
- Lucent-liver sign refers to the diffuse radiolucency in hepatic area seen on supine radiograph when the air collection is in anterior perihepatic location.
- Football sign (*American football*) refers to ovoid-shaped radiolucency oriented in the sagittal plane on supine radiograph in cases of massive pneumoperitoneum. Sometimes, a linear soft tissue dense opacity is noted in midline location in the superior part of the radiolucency, representing falciform ligament and a similar opacity in midline inferior part corresponding to median umbilical ligament.

Presence of gas-filled small and large bowel loops usually up to the rectal region denotes paralytic ileus.

Basic indications for abdominal ultrasonography:

- Evaluation of abdominal cavity for early detection of life-threatening conditions as acute circulatory failure
- Extended focused assessment with sonography for trauma (EFAST) for rapid identification of free fluid in the body cavities of the trauma patients who are hemodynamically unstable
- Detection of acute fluid/pus collections
- Guiding insertion of the drain tubes for fluid collections
- Guiding percutaneous procedures as percutaneous transhepatic biliary drainage (PTBD) in patients with severe obstructive jaundice
- Doppler sonography may be used to determine the deep venous thrombosis in limbs, hepatic venous/IVC thrombosis in acute hepatic failure and graft versus host reaction in transplanted organs.

by mansdocs.com

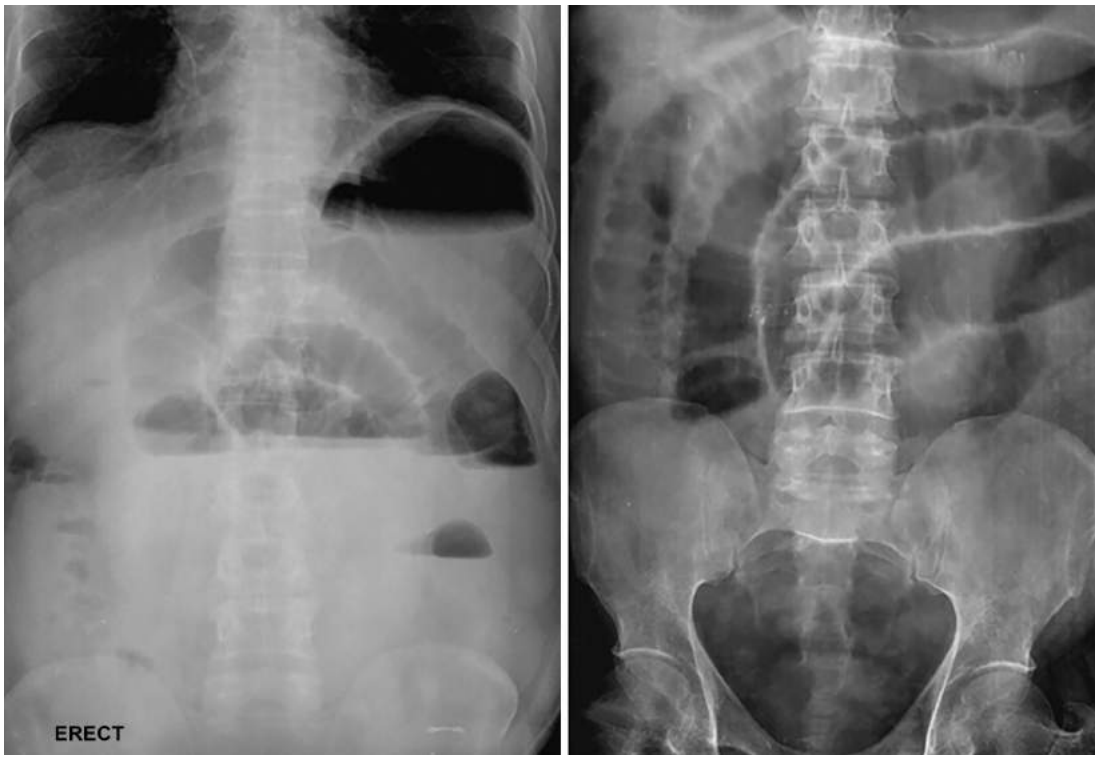


Fig. 20: Anteroposterior radiograph of abdomen in erect and supine postures shows multiple, dilated small bowel loops and air-fluid levels in case of acute intestinal obstruction.

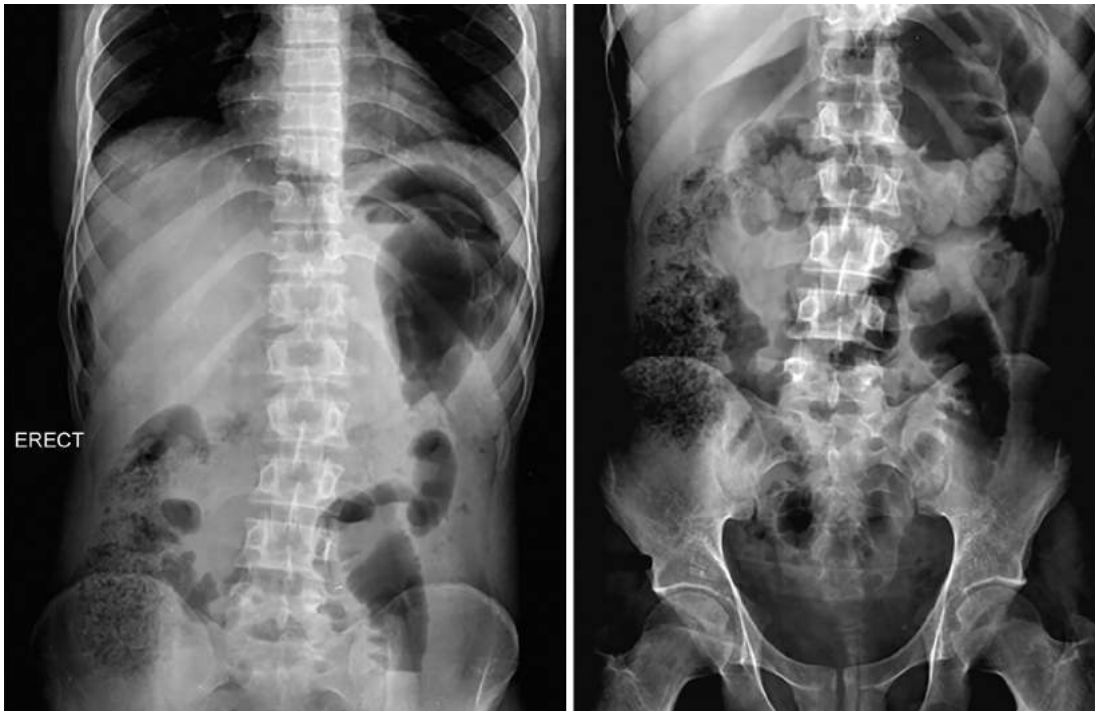


Fig. 21: Anteroposterior radiograph of abdomen in erect and supine postures shows free air under left dome and central tendon of diaphragm, right perihepatic and infrahepatic spaces and in between the bowel loops.

by mansdocs.com



Fig. 22: Anteroposterior radiograph of abdomen in case of paralytic ileus.

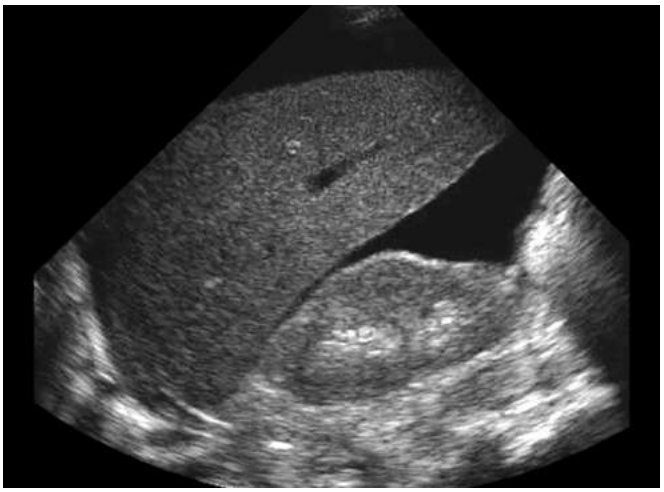


Fig. 23: Ultrasound scan shows free fluid in the peritoneal cavity (Morison's pouch).

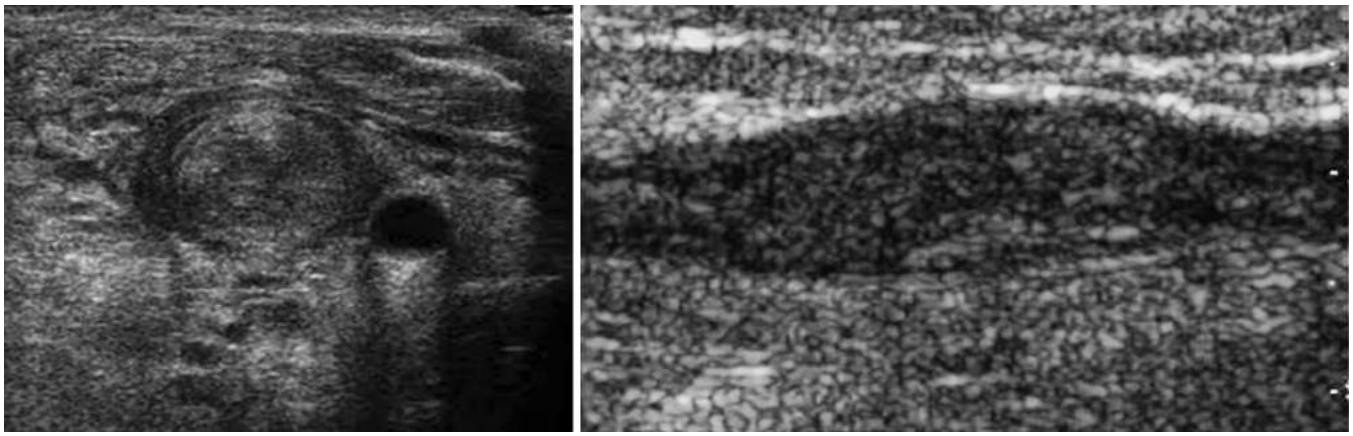


Fig. 24: Ultrasound images in transverse section and longitudinal section showing thrombosis of vein.

Systematic approach in extended focused assessment with sonography for trauma:

- Evaluate the four quadrants of the abdomen (look for fluid collections)
- Evaluate bilateral pleural spaces (look for fluid and air collection)
- Evaluate the pericardial space (look for fluid collection).

Trendelenburg position is useful to visualize free fluid in the perihepatic and perisplenic fluid and reverse Trendelenburg position to visualize free hem thorax or free pelvic fluid. Perinephric fat in obese patients may be misinterpreted as free peritoneal collection (Fig. 23).

Ultrasonography along with duplex/triplex Doppler technique plays a critical role in early detection of deep vein thrombosis (DVT) in ICU patients due to its noninvasive nature, in addition to its bedside portability and non-requirement of contrast medium. However, Doppler study in ICU patients is often suboptimal leading to its relatively lower sensitivity and specificity compared with venography. With Doppler, upper and lower limb veins including iliac veins and IVC can be studied.

In acute thrombosis, the affected vein is dilated and non-compressible with lack of color flow, Doppler spectra and respiratory phasicity. Partial thrombosis is noted as a variable filling defect in color flow within the lumen of vein, while complete thrombosis is noted as complete absence of color flow. Serial studies performed in high-risk, asymptomatic patients may provide a cost-effective procedure of reducing the incidence of pulmonary thromboembolism in ICU patients (Fig. 24).

by mansdocs.com

SECTION 12

Mechanical Ventilation

by mansdocs.com

by mansdocs.com

CHAPTER

70

Respiratory Mechanics: Basics

Rajesh Pande, Vipin Kauts

INTRODUCTION

During spontaneous breathing, the airflow begins at the mouth or nose and ends at the alveolar level. The transpulmonary pressure, the pressure difference between intrapulmonary and intrapleural pressures is responsible for the movement of air in and out of the lungs.

During inspiration, the diaphragm and external intercostal muscles contract, increasing the volume of the thoracic cavity. This causes the intrapleural pressure to become more negative, which increases the transpulmonary pressure, causing the lungs to expand. The expansion of the lungs lowers the intrapulmonary pressure below atmospheric pressure. Air, following its pressure gradient, now flows into the lungs.

During machine ventilation, the air flows from higher pressure at one end (tube end) to a lower pressure at the other end (alveoli). The changes in lung volume are caused by the resultant pressure changes. Respiratory pressures are measured in cm. of H_2O with zero (0) as baseline (= atmospheric pressure, i.e. 760 mm Hg).

Transthoracic pressure determines the lung volume responsible for maintaining alveolar distension and is also known as alveolar distending pressure. All modes of positive pressure ventilation try to increase this pressure by increasing the alveolar pressure (P_A) as the body surface remains atmospheric but the airway pressure (P_{AW}) becomes positive.

Peak Airway Pressure

During intermittent positive pressure ventilation (IPPV), the pressure at machine end gradually rises to a peak pressure. It is also called peak airway pressure or peak inspiratory pressure (PIP). It represents the sum of pressure required to overcome the airway resistance and to inflate the alveoli (Fig. 1).

Plateau Pressure

Pressure measured after a breath has been delivered to the patient and before exhalation has begun. It stabilizes and plateaus at a certain point. Exhalation is prevented by the ventilator for a brief moment, 0.5–1.0 seconds. To perform it, inspiratory pause (inflation hold) is used. It is like holding a breath at the end inspiration, when the pressure

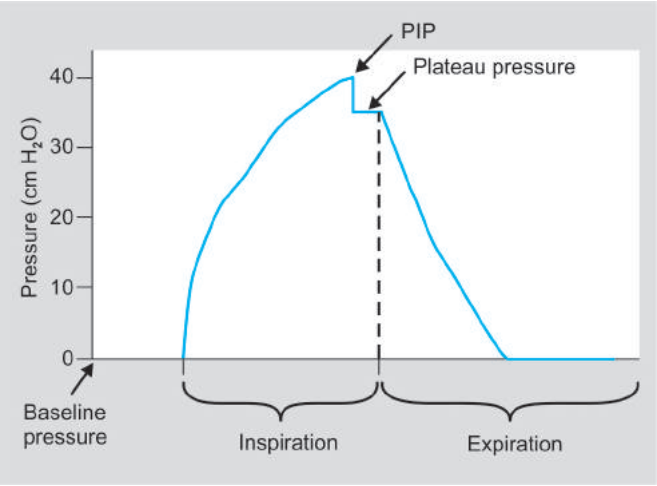


Fig. 1: Upper airway pressure during a positive pressure breath. Plateau pressure can be measured during a breath holding maneuver. (PIP: Peak inspiratory pressure).

by mansdocs.com

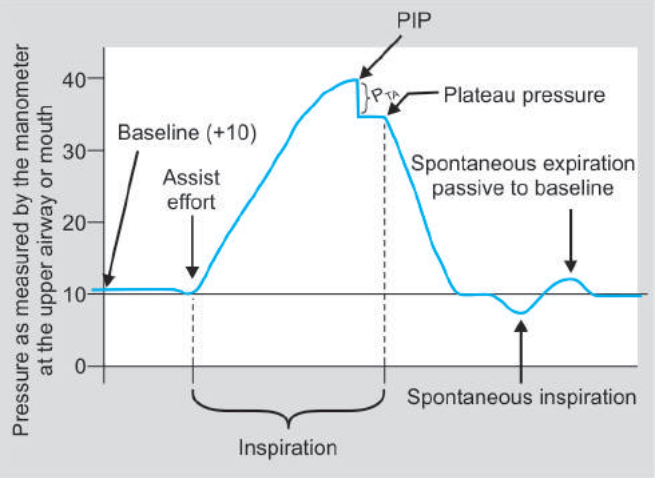


Fig. 2: Airway pressure during a positive pressure breath and a spontaneous breath. (PEEP 10 cm H_2O).
(PIP: Peak inspiratory pressure; PTA: Transairway pressure; PEEP: positive end expiratory pressure).

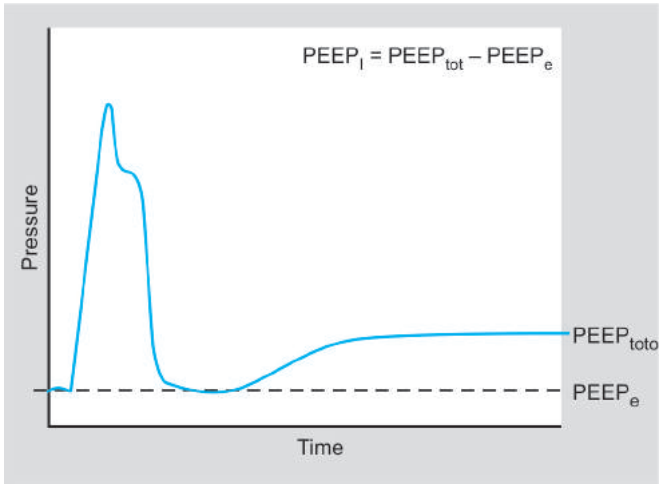


Fig. 3: Intrinsic PEEP = Total PEEP – Set PEEP.

inside the mouth and alveoli is equal (no gas flow). At this point, plateau pressure, P_A or intrapulmonary pressure represent the same (Fig. 2).

Intrinsic Positive End Expiratory Pressure

The rate at which lung empties is determined by the elastic recoil (inverse of compliance) of the lungs and the resistance of the airways. The lower the elastic recoil forces (stiff chest) and higher the resistance to airflow (asthmatics), the slower the lung will empty. If exhalation is incomplete when the next breath is delivered, it results in a greater volume of air being delivered than exhaled, resulting in gas trapping (breath stacking). The trapped air exerts a positive pressure at end exhalation, which is referred to as intrinsic positive end expiratory pressure (PEEP) or auto PEEP (Fig. 3).

Quantitative measurement of intrinsic PEEP can be obtained in an apneic patient by using the expiratory pause hold control on the ventilator. This allows equilibration of pressures between the alveoli and the ventilator allowing the total PEEP to be measured.

Static auto PEEP measures the average pressure at end expiration in lung units communicating with the mouth (+ 10 in this example) (Fig. 4).

By contrast, dynamic auto PEEP will measure the open lung unit with the least auto PEEP (+5 in this example).

Static and dynamic methods may underestimate auto PEEP because they do not measure the level of auto PEEP in lung units which do not communicate with the mouth.

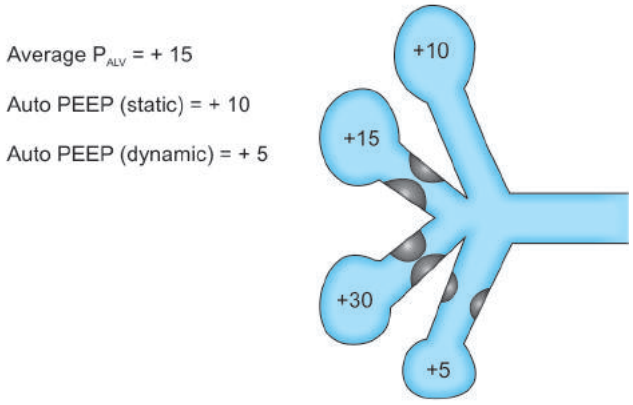


Fig. 4: Static and dynamic auto PEEP may differ.
(PEEP: Positive end expiratory pressure; P_{ALV}: alveolar pressure).

This situation could occur in a patient with asthma where mucus obstruction of the airways is a prominent feature (+30 in this example).

LUNG CHARACTERISTICS

Two Forces Oppose the Inflation of Lungs

Elastic forces (due to elastic properties of the lungs and thorax) and frictional forces (resistance caused by tissue and organs as they move and resistance to gas flow through the airways).

Compliance

Compliance is a measure of distensibility. A balloon that is easy to inflate is very compliant, whereas one

by mansdocs.com

that is hard to inflate is noncompliant. Elastance is the tendency of a structure to return to its original form after being stretched.

Compliance is the opposite or inverse of elastance (C = 1/e) and is, therefore, a measure of the elastic forces opposing lung inflation. It is defined as the change of volume that corresponds to the change in pressure.

C = δV/δP, where δ stands for change.

Normal compliance of the lungs is the sum of compliance of both lungs and adjacent thoracic structures. In spontaneously breathing patients, the total compliance is 0.1 L/cm H_2O, and varies on posture, position and level of consciousness of the subject. It can range from 0.05 to 0.17 L/cm H_2O (50–170 mL/cm H_2O). In ventilated patients, the compliance will vary from 40–50 mL/cm H_2O in males to 35–45 mL/cm H_2O in females to as high as 100 mL/cm H_2O in both sexes.

When compliance is measured during conditions of no flow, it is called static compliance. It can be measured by causing an inspiration hold. The plateau pressure minus PEEP is taken as the pressure change, and expiratory tidal volume is measured. ($C_L = V_T$/ Plateau pressure–PEEP).

Technically, it represents two compliances in series (lung and chest wall), but since the thoracic compliance is generally unchanged in a ventilated patient, it is not taken into consideration.

Elastance

Elastance is the reciprocal of compliance, and measures the recoil or retractive forces in the lung.

E = 1/C = δP/δV.

It is generated by: (a) tissue forces: the lung contains large amounts of collagen and elastin, which tend to provide retractile forces and (B) surface tension.

Hysteresis

Hysteresis is a phenomenon, where the lung becomes more compliant upon expiration than inspiration. Inflation causes surfactant to pass from the cell to the surface, where it reduces surface tension. Upon expiration, the surfactant is already present where it is needed, and so there is increased compliance (Fig. 5).

This is because the inflation maneuver requires a level of pressure to initially recruit collapsed alveoli and stabilize the surfactant layer. However, during deflation, this extra pressure is not needed to prevent derecruitment. Therefore, ventilation on the deflation limb is mechanically advantageous and is the rationale behind sigh breaths, recruitment maneuvers and PEEP.

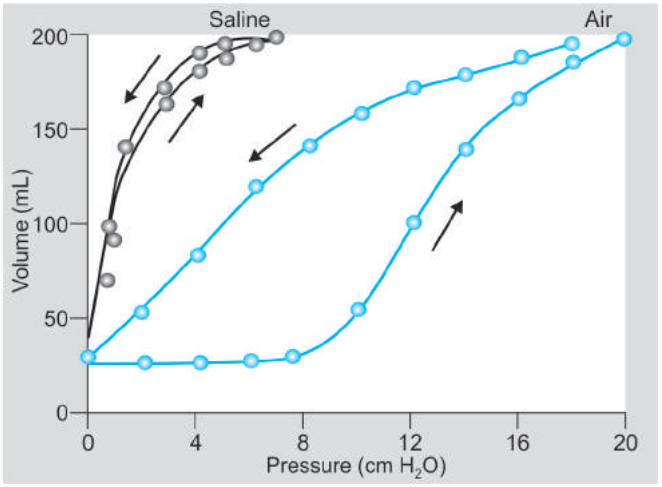


Fig. 5: Pressure versus volume loop.

Resistance

Frictional forces or resistance is due to the anatomical structure of the conductive airways and the tissue resistance of lungs and adjacent structures (abdominal organs, rib cage, diaphragm). The movements of these organs result in resistance, and ascites etc. would further increase it.

Resistance = Airway resistance + Tissue resistance (lungs, thoracic cage, abdominal organs, diaphragm).

Airway resistance = PIP–P plateau/Flow.

e.g. 40–25 cm H_2O/1 L/sec = 15 cm H_2O/L/sec.

Normal value: 0.6–2.4 cm H_2O/L/sec.

Intubated: 6 cm H_2O/L/sec or higher.

Emphysema, asthma: Range from 13–18 cm H_2O/L/sec.

It is the resistance of the airways, which is most commonly evaluated during mechanical ventilation. The airflow into the airways depends on gas viscosity, gas density, length and diameter of the tube and the flow rate of gas through the tube. In clinical situation, the two important variables are airway diameter and gas flow rate.

The Decrease in Airway Diameter

The airway diameter decreases bronchospasm, increased secretions, with mucosal edema and a small endotracheal tube or tube kinks. The flow rate of gas is generally well controlled by the ventilator. The gas flow during inspiration causes slight expansion of the airways due to the pressure exerted and the gas molecules, which collide with each other to slow down the gas flow (viscous resistance).

Disadvantages of increased airway resistance: Pressure for breathing is lost to the airways and never reaches the alveoli (with less pressure, less volume of gas is available for gas exchange). More force must be exerted to try

by mansdocs.com

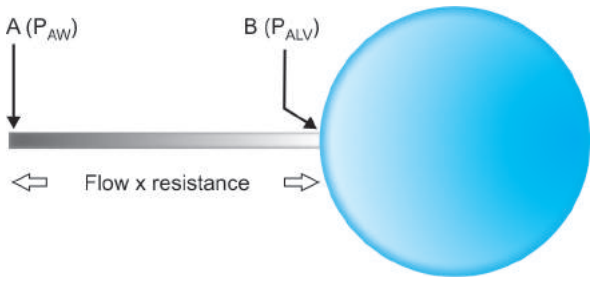


Fig. 6: Relation between airway resistance and alveolar pressures. (P_{AW}: Airway pressure; P_{ALV}: Alveolar pressure).

and get the gas to flow through the obstructed airway. To achieve it, spontaneously breathing patients use accessory muscles to try to breathe; during mechanical ventilation, the P_{AW} needs to be raised to achieve the tidal volume (Fig. 6).

Pressure at point B (P_A) = (Volume/Compliance) + PEEP

Pressure at point A (mouth pressure) = (Flow × Resistance) + (Volume/Compliance + PEEP).

Measurement of P_{AW} in intubated patients:

$P_{TA} = PIP–P_A$

If peak pressure is 25 and plateau pressure is 20 cm H_2O, P_{TA} = 05. It is the pressure lost to the airways because of airway resistance (which is normal pressure lost if a proper size endotracheal tube is placed).

If peak pressure increases to 40 and plateau pressure is 25, the pressure lost is 15 cm H_2O, which is high and indicates, rise in airway resistance. In both situations, the gas flow is constant (60 L/min or 1 L/sec) and the R_{AW} = 5 cm/H_2O/L/sec and 15 cm/H_2O/L/sec in the second situation.

Concept of Sow, Fast Alveoli, Time Constants

Changes in compliance and resistance are not uniformly distributed in the lung parenchyma. Some parts may be normal, others may be affected by increased airway resistance and still others by low compliance or by a combination of these factors. Therefore, during inhalation or exhalation, different areas of lung empty and fill faster or slower than others. Imagine, each small unit of lung is like a inflatable balloon attached to a short soda straw. Now the amount of air a balloon receives will depend on the compliance of balloon and the airway resistance of the soda string (assuming all other factors, such as gas flow, are constant). We can have three types of lung filling units:

(1) Normal: Fill with a large volume during a reasonable time. Filling is nearly complete before exhalation begins.

(2) Stiff units (low compliance) (fast alveoli): These fill quickly but with much smaller volume and empty quickly.

(3) Units with increase airway resistance (slow alveoli): Fill very slowly, with a smaller volume than a normal unit (more so if inspiratory time is short). In fact, the rest of lung units could very well begin exhalation before these high resistance units have received full volume.

Time Constant

The rate at which individual units fill is called the time constant. A time constant is the product of compliance and resistance.

e.g. If R_{AW} is 1 cm/H_2O/L/sec and compliance is 0.1 L/cm H_2O, the time constant will be 0.1 sec.

One time constant allows 63% of either inspiratory or expiratory phase to occur. Two time constants allow 86%, three time constants 95%, four time constants about 98% of either phase to occur. Five time constants theoretically allow inspiration and exhalation to occur completely.

In the above example, five time constants would equal 5 × 0.1 = 0.5 sec, which is the time in which a normal lung unit could completely empty or fill. Concept of time constants is important in mechanical ventilation. An inspiratory time setting less than three time constants may cause incomplete delivery of tidal volume. Similarly, an expiratory time less than four time constants may lead to incomplete emptying of lungs and can result in increase functional residual capacity (FRC) and auto PEEP.

Short time constants are the product of either normal or low airway resistance or low compliance or a combination of both. Slow filling units have long time constants and take more time to fill and empty. Long-time constants are the product of either increased airway resistance or increased compliance or both. Fast filling units have short time constants and take less time to fill and empty.

BIBLIOGRAPHY

1. Bekos V, Marini JJ. Monitoring the mechanically ventilated patient. Crit Care Clin. 2007;23(3):575-611.
2. Harris RS. Pressure-volume curves of the respiratory system. Respir Care. 2005;50(1):78-98.
3. Hickling KG. The pressure-volume curve is greatly modified by recruitment. Amer J Resp Crit Care Med. 1998;158(1): 194-202.
4. Lichtwarck-Aschoff M, Kessler V, Sjöstrand UH, et al. Static versus dynamic respiratory mechanics for setting the ventilator. Br J Anaesth. 2000;85(4):577-86.
5. Santanilla JI, Daniel B, Yeow M. Mechanical ventilation. Emerg Med Clin North Am. 2008;26(3):849-62.

by mansdocs.com

CHAPTER

71

Principles of Mechanical Ventilation

Rajesh Pande, Maitree Pande

ACUTE RESPIRATORY FAILURE

Acute respiratory failure (ARF) occurs if a disease process or pharmacology intervention results in impairment of the capacity of respiratory muscles and increased ventilation requirement above the muscle capacity resulting in increased workload toward work of breathing (WOB). When oxygen therapy and non-invasive ventilation are inadequate to improve the situation, intubation and initiation of mechanical ventilation become necessary.

TARGETS OF VENTILATION

Ventilator generates flow and volume to provide adequate alveolar ventilation with minimal work of breathing (WOB). The power required for ventilation is provided by contraction of respiratory muscles. The phrenic nerve controls the timing and intensity of breathing with inputs from the chemoreceptors, pulmonary stretch receptors and variation in metabolic demands.

POSITIVE PRESSURE VENTILATION

To understand how ventilator delivers a breath, it is important to understand what initiates a breath, limits it and how changer from inspiration to expiration occurs.

What Initiates a Breath (Trigger Variable)

- Either by predetermined time interval (control modes)
- Or when a predetermined sub-baseline pressure is created (assist mode).

Pressure trigger: Patient needs to decrease pressure in the respiratory circuit at a preset threshold level.

Flow trigger: Patient needs to generate a preset amount of inspiratory flow.

Inspiratory effort necessary to trigger a breath has been estimated to be about 17% and about 12% of the total inspiratory effort during pressure and flow trigger, respectively.

What Limits the Gas Delivery (Limit Variable)

- *Volume limit*: Provides flow, pressure and time to deliver a preset volume
- *Pressure limit*: Provides flow, volume and time required to maintain a preset pressure
- *Flow limit*: Provides pressure, volume and time to reach a preset flow in the ventilator circuit.

What Terminates the Breath (Cycle Variable)

Changeover from inspiration to expiration:

- *Volume cycled*: Changeover occurs when a preset volume is delivered.
- *Time cycled*: Changeover occurs when a preset time interval has elapsed.
- *Flow cycled*: Changeover occurs when flow has reduced to a predetermined level.
- *Pressure cycled*: Changeover occurs when pressure reaches a predetermined level.

These three variables can affect the physiological requirements of breathing that includes Ventilatory drive (when inspiration starts), Ventilatory requirement (how much volume and flow are required and the timing of

by mansdocs.com

internal circuitry generating respiratory rhythm. If pressure rise time is modified at the beginning of inflation (inspiratory pressure slope), it can influence expiratory threshold by its effect on peak inspiratory flow. The rapid pressure rise may decrease the WOB.

Assist/Controlled Mechanical Ventilation

Patient is allowed to set his/her own respiratory rate by activating the inspiratory trigger function (as safety measure, if no spontaneous effort occurs, the ventilator will deliver controlled breath at a preselected breath rate). This mode is patient initiated, time cycled and flow and volume (Assist controlled mechanical ventilation (A/CMV) or pressure limited (A/PCV).

A/PCV with flow trigger is a better option. It improves patient ventilator outcome, due to higher inspiratory peak flow as compared with volume cycled.

Assist/controlled mechanical ventilation and synchronized intermittent mandatory ventilation (SIMV) share the same limitation that during patient triggered breaths, effort does not cease with the onset of gas delivery, and the total inspiratory workload during A/CMV may even exceed the work performed during spontaneous breathing.

Pressure Regulated Volume Control (PRVC)

It is a controlled mode that is able to share theoretical advantage of constant pressure with guarantee of delivering a preset tidal volume (VT). It consists of a closed loop algorithm, which, based on measurement of static compliance of the respiratory system, changes the level of applied volume.

Pressure Support Ventilation

Patient is able to modulate the ventilatory pattern through changes in inspiratory efforts. It is patient initiated, flow cycled mode. Cycling occurs when flow is reduced to 25% of the peak flow. The respiratory rate is controlled by the patient.

Issues with Current Ventilator in Spontaneously Breathing Patients

A very important issue is that the initiation of ventilator breath delivery (triggering) should coincide with the initiation of patient effort. There are three problems—to avoid auto triggering a certain level of insensitivity must be put in the patient effort sensor. Second is the slow system responsiveness—even when the patient effort has been sensed; demand valve systems have a certain inherent delay (up to ≈ 100 ms) before they actually open and achieve target flow into the airway. Third and a very important aspect is that ventilator breath termination does not correlate with termination of patient effort and the breath lasts longer than patient effort (cycling delay) and an inadequate expiratory time can occur leading to air trapping. The breath terminates before the patient effort is finished (premature cycling) and the patient may be left demanding additional flow without any being delivered, leading to imposed load and double triggering.

A novel approach to improve the patient ventilator synchrony includes two new ventilatory modalities: (i) proportional assist ventilation (PAV) (available in Puritan Bennett PB 840 ventilator) and (ii) neurally adjusted ventilatory assist (NAVA) (by Maquet SERVO-i ventilator).

Proportional assist ventilation (PAV) is driven by circuit pressure and flow signals. It is a spontaneous breathing mode that offers assist to the patient in proportion to the patient's effort. The closed-loop PAV automatically measures and adjusts for changes in the patient's respiratory mechanics and could be considered as equivalent to an adaptive pressure support. Closed-loop ventilation logic in PAV is based on the work of breathing (WOB). In this mode, the patient's respiratory center in his brain is in charge of all aspects of ventilatory rate, depth and pattern. The major components of WOB are: resistance of the patient's airways, resistance of the artificial airway, lung and chest wall compliance. Here, the clinical does not set flow, volume, pressure or time targets, but sets a "GAIN" (percentage of work that the ventilator should do) on patient-generated flow and volume. It boosts the sensed patient effort according to the clinician set proportion. Greater the patient effort, greater the delivered pressure, flow and volume.

Neurally adjusted ventilatory assist (NAVA): It does not control the ventilator from pressure and flow signals, but goes to the "source" and uses a diaphragmatic electromyographic signal to trigger, guide flow, and cycle ventilatory assistance. Patient ventilator communication is thus more direct. Electromyographic sensor is placed in the esophagus at the level of the diaphragm and the ventilator breath triggering is simultaneous with the onset of phrenic nerve excitation of the inspiratory muscles. Like PAV, ventilator flow delivery is driven by a clinician set gain on the EMG signal, but unlike any other mode, breath cycling with NAVA is linked to the cessation of

by mansdocs.com

inspiratory muscle contraction. Positive pressure is applied to the airway opening in proportion to the electrical activation of the diaphragm (EAdi). With NAVA, ventilator support is initiated when the neural drive to the diaphragm begins to increase. As the EAdi progressively increases, the assist increases proportionally and the pressure delivered by the ventilator is cycled-off when the EAdi is ended by the respiratory centers. The amount of assist delivered during NAVA depends on a proportionality factor, the so-called "NAVA level". NAVA level defines the magnitude of pressure delivered for a given EAdi. When the NAVA level is changed, the resulting pressure delivered by the ventilator depends on how the respiratory afferents modulate the neural output to the diaphragm.

by mansdocs.com

CHAPTER

72

Basic Modes of Ventilation

Maitree Pande, Rohini Arora

INTRODUCTION

Mechanical ventilation reverses the negative pressure spontaneous breathing to positive pressure breathing with its effects on cardiorespiratory system. As in the spontaneous breathing, inspiration is an active process where ventilator spends the energy toward work of breathing in controlled mode (total ventilatory support) or the work is shared between the machine and the spontaneously breathing patient (partial ventilatory support). Expiration is a passive process.

A positive pressure ventilator has four important elements.

1. An internal source of pressurized gas [including a blender for air and oxygen to give desired fractional inspired oxygen (FIO_2)]
2. Valves (inspiratory and expiratory) and the ventilator circuit.
3. Microprocessor control system, which controls delivery and monitoring of breath and alarms. It works on user inputs and information provided by sensors for pressure and gas flow.
4. A mechanism for patient ventilator synchronization (ventilator identifies a patient's breathing effort and delivers with it). This is also called the trigger: inspiratory trigger could be flow or pressure trigger, whereas the expiratory trigger is generally flow based, which stops inspiration and cycles machine to expiration.

The baseline pressure over which a breath is delivered could be either zero or above baseline (positive) termed as PEEP or CPAP.

The ventilatory breath cycle can be best understood by dividing a machine breath into three components: breath initiation inspiration limit and cycling (changeover from inspiration to expiration) (Table 1). This is the basis of classifying the ventilatory modes. Breath could be initiated either by the patient (spontaneously breathing patient) or by the machine (relaxed, sedated or non-breathing patient) (Figs. 1 to 6). Patient initiated breath is by an inspiratory trigger (pressure or flow). Patient initiated modes are: Assist control, assisted spontaneous and spontaneous breaths (Figs. 7 and 8).

Pressure trigger: Ventilator senses the patient's breathing effort by sensing a decrease in pressure below the baseline. Normally set at -2 to -3 cm H_2O.

Flow trigger: A bias flow (airflow) continues to run in the ventilator circuit throughout the respiratory cycle and the

Table 1: Components of ventilatory breath cycle.

Breath type	*Breath initiation*	*Inspiratory limit*	*Cycling to expiration*
• Controlled	• Machine	• Volume or pressure control	• Time cycled (Inspiratory time setting)
• Assist control	• Patient initiated trigger, respiratory rate (RR) set by machine	• Pressure control	• Time cycled (Inspiratory time setting)
• Assist spontaneous	• Patient initiated trigger	• Pressure control (pressure support setting)	• Flow trigger
• Spontaneous	• Patient initiated trigger	• Pressure support (PEEP/CPAP setting)	• Flow trigger

by mansdocs.com

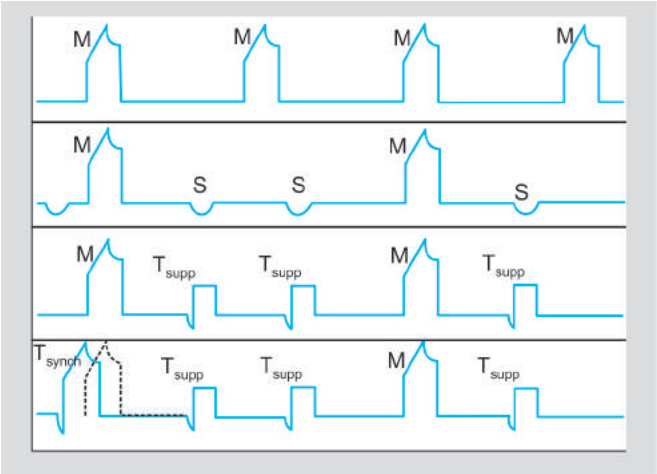


Fig. 1: Mandatory, spontaneous and triggered inspiratory cycling.

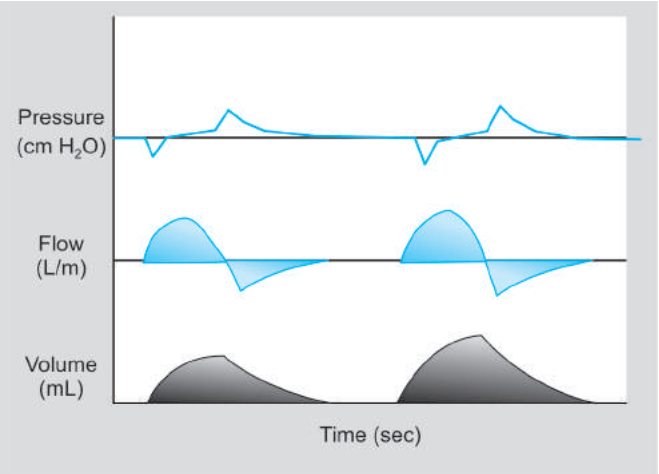


Fig. 2: Spontaneous breathing.

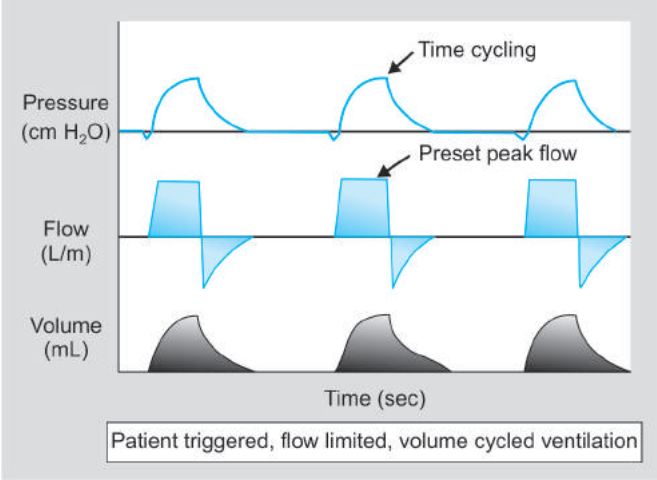


Fig. 3: Assisted mode: Volume-targeted ventilation.

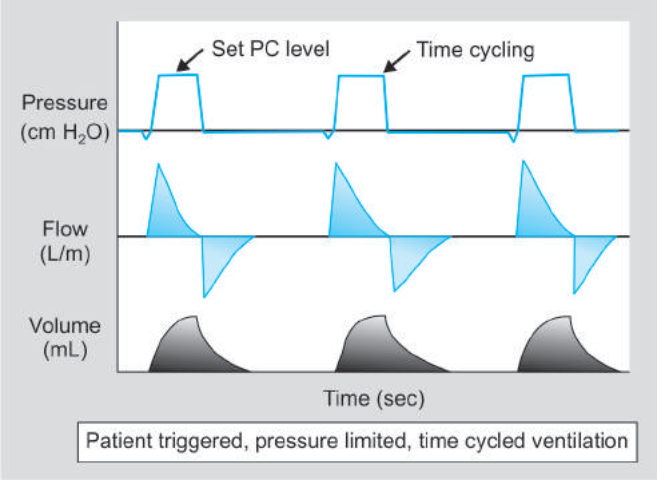


Fig. 4: Assisted mode: Pressure-targeted ventilation. (PC: Pressure control).

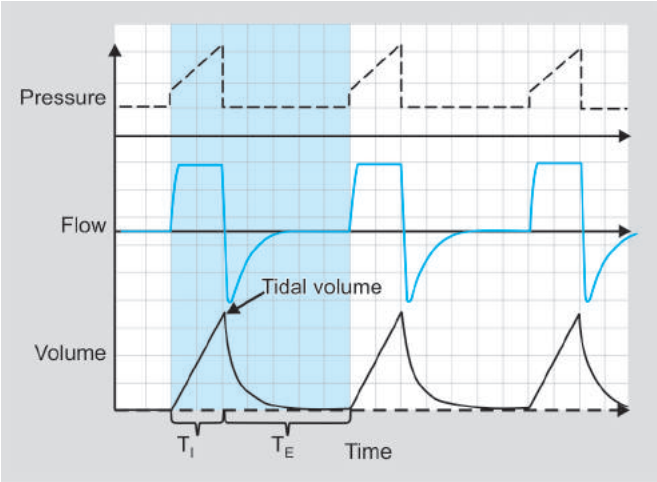


Fig. 5: Volume controlled ventilation.

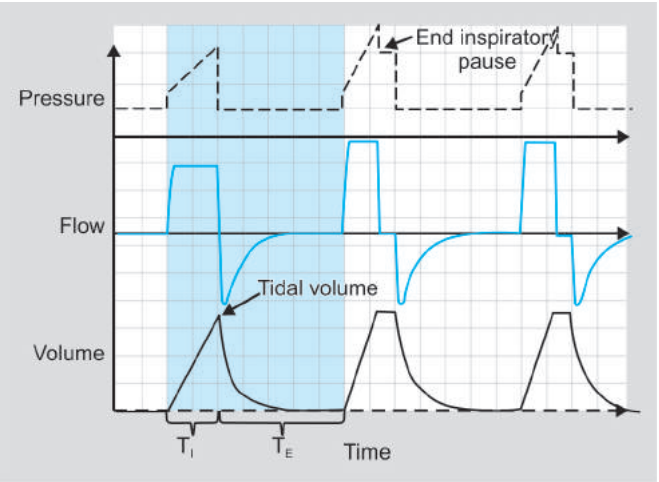


Fig. 6: Volume control with inspiratory pause.

by mansdocs.com

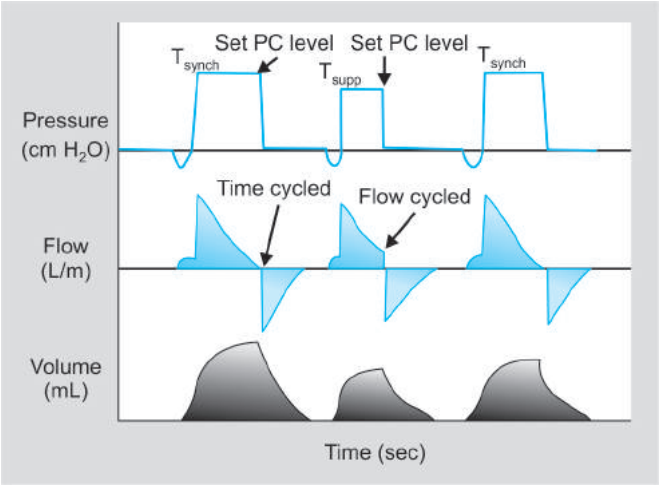


Fig. 7: SIMV +PS—Pressure-targeted ventilation.

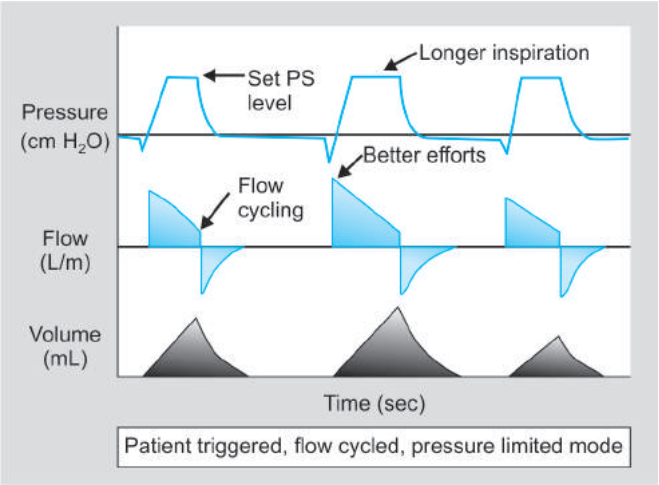


Fig. 8: Pressure support ventilation.

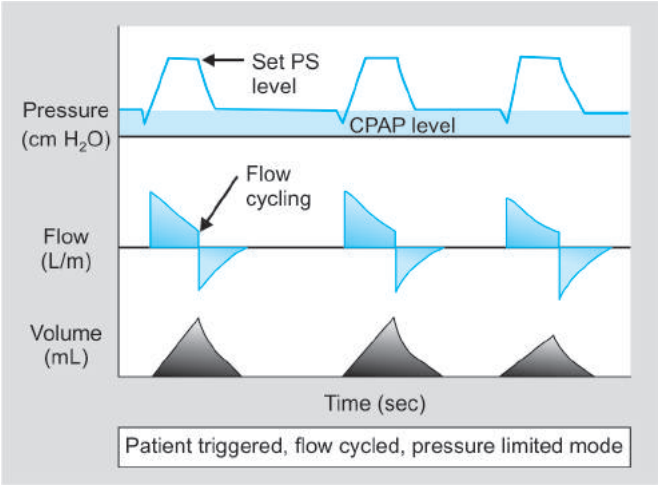


Fig. 9: CPAP +PSV.

moment the patient initiates a breath by contracting his inspiratory muscles, he draws from the bias flow. This is sensed by the ventilator (flow trigger), which responds by increasing airflow to inspiratory levels. Trigger sensitivity should be high to reduce ventilator response delay, which improves synchrony and patient comfort, but should not be too high as it may start auto triggering (self cycling). Normally set between 1–3 L/min.

Cycling is changeover from inspiration to expiration. It could happen after a prefixed time interval (Ti) has elapsed (control modes). This can be set in different ventilators by different means—I:E ratio, duty cycle (Ti %) or alternately, in spontaneously breathing patients, when the inspiratory flow decrease to some level (25% of peak flow) called flow cycling as in the pressure support mode.

Ventilator modes are specific ventilatory logic based on the respiratory cycle variables discussed above.

Volume-Control Mode

Tidal volume (Vt) is preset and breaths are either controlled or assist-controlled, depending on the lack or presence of patient's spontaneous breathing effort and the inspiratory trigger. When the inspiratory trigger is active, volume control mode is called as assist control ventilation (*see* Figs. 2 and 3).

Pressure Control Mode

Inspiration is promoted by a pre-set pressure (Pinsp). The breaths like in volume control are either controlled or assist-controlled (*see* Fig. 4)

SIMV mode (Synchronized Intermittent Mandatory Ventilation)

This mode alternates assist control volume or pressure breaths—SIMV-VC/SIMV-PC (delivered according to a user-set mandatory frequency) with spontaneous breaths. The spontaneous breaths can be either supported (when pressure support is set above zero- SIMV + PS) or fully spontaneous (when pressure support is set to zero, SIMV only). In this mode, the machine breath is synchronized to be delivered with the patient's spontaneous breathing. The ventilator becomes sensitive to patients' breathing effort for a few microseconds before the control breath delivery and gives in synchrony with the patient's effort (if he is breathing, otherwise it simply works as a control mode) (Figs. 9 and 10).

by mansdocs.com

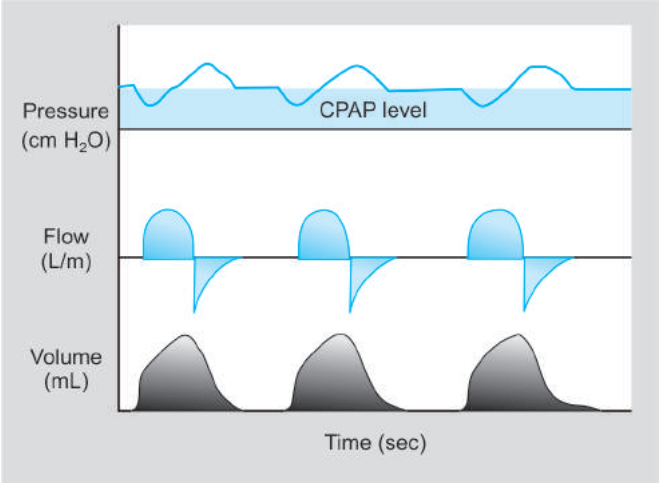


Fig. 10: Continuous positive airway pressure.

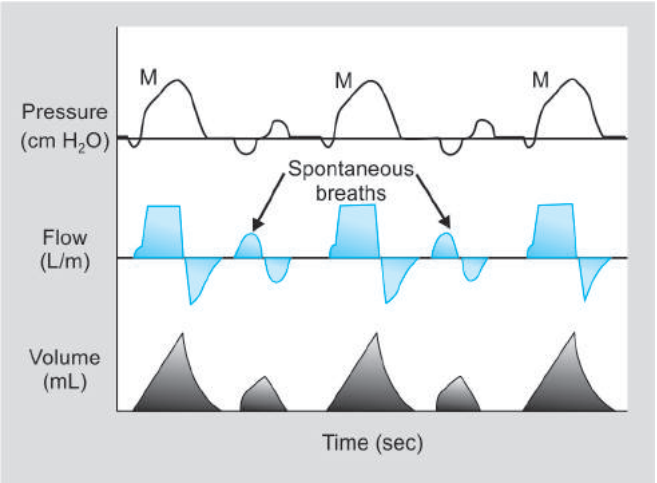


Fig. 11: Synchronized intermittent mandatory ventilation (SIMV)—Volume-targeted ventilation.

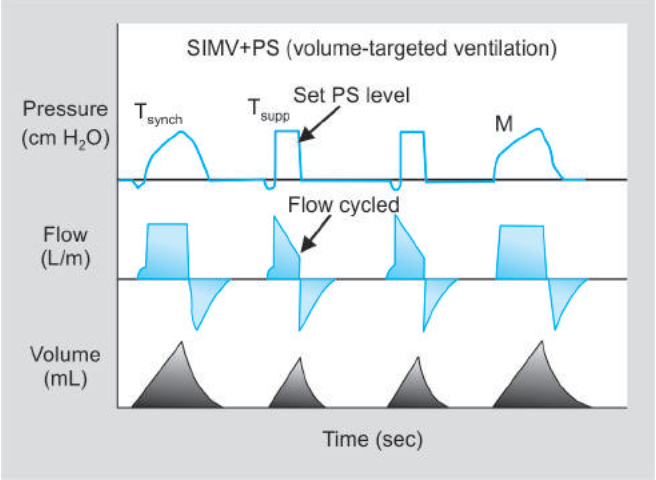


Fig. 12: SIMV + PS—Volume-targeted ventilation.

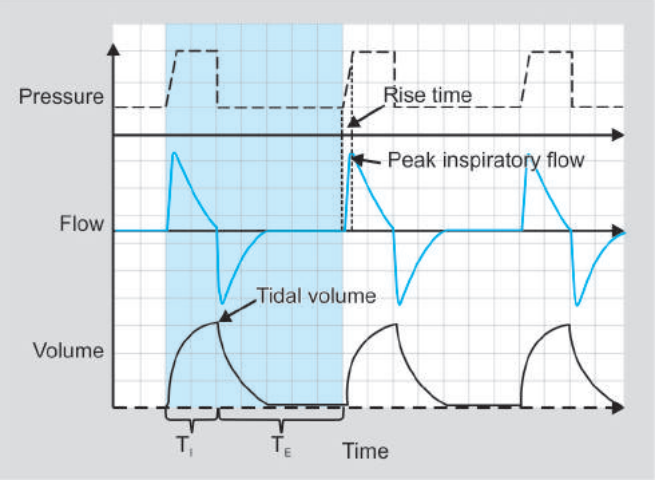


Fig. 13: Pressure control ventilation.

Pressure Support Mode

The spontaneous breaths are supported by a preset pressure. What we set is the Pressure support level, flow or pressure sensitivity, continuous positive airway pressure (CPAP) and the pressure limit. The frequency is decided by the patient (Figs. 11 and 12).

CPAP Mode

All breaths are fully spontaneous, and the inspiratory pressure is ideally equal to the set CPAP positive end-expiratory pressure (PEEP) level. Only the CPAP levels are set and the frequency and tidal volume depend on patient effort (Fig. 13).

BIBLIOGRAPHY

1. In: Cairo JM (Ed). Pilbeam's Mechanical Ventilation: Physiological and Clinical Applications, 5th edition. Elsevier; 2012.
2. In: Chang DW (Ed). Clinical Application of Mechanical Ventilation, 3rd edition. Delmar Cengage Learning; 2006.
4. In: MacIntyre NR, Branson RD (Eds). Mechanical Ventilation, 2nd edition. WB Saunders; 2008.
3. Kapadia F. Mechanical ventilation: simplifying the terminology. Postgrad Med J. 1998;74 (872):330-5.

by mansdocs.com

CHAPTER

73

Ventilator Graphics

Rajesh Pande, Puneet Khanna

INTRODUCTION

Mechanical ventilation often involves complicated medical and/or surgical problems in critically sick patients that poses major challenges for intensivists managing the intensive care unit (ICU). With the availability of newer mechanical ventilators, patient-ventilator interaction is now optimally displayed in the form of graphic information as a part of standard equipment. Graphics can aid clinicians in deciding which ventilator mode is most appropriate, or in fine-tuning the settings for a given mode in order to achieve the best combination for the patient. This objective makes it essential for all intensivists to understand the basics of ventilator waveforms and take appropriate management decisions.

VENTILATOR WAVEFORMS

Waveforms usually plot one of the three parameters (pressure, flow, or volume) against time. Conventionally, time is plotted on the horizontal (x) axis and the other parameter is plotted on the vertical (y) axis. Time, pressure, and flow are the most common triggering mechanisms in mechanically ventilated patients.

Pressure-Time Waveform

Figure 1 shows a pressure-time graphic of three breaths.

The first breath (A) shows a negative deflection, representing the patient's triggering of the breath. The ventilator sensitivity is set so that an inspiratory effort by the patient will trigger the delivery of a breath.

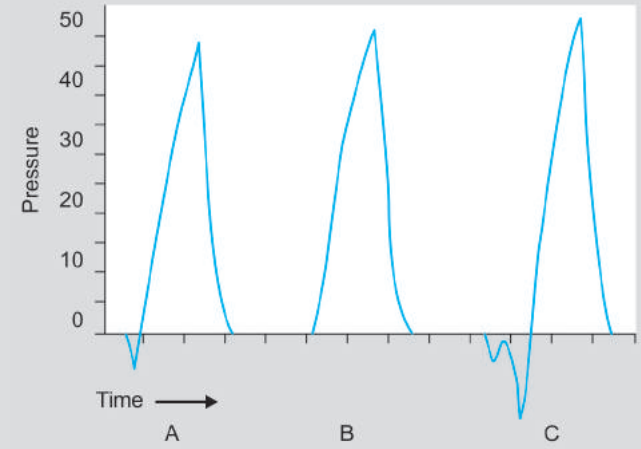


Fig. 1: Pressure-time graphic waveform.

The second breath (B) is not triggered by the patient, but is, instead, initiated by the machine (time triggered).

The third breath (C) shows an improperly set sensitivity; the patient is having to generate a large negative inspiratory pressure before the trigger point is reached and a breath is given. This increases the work of breathing and is very uncomfortable for the patient. Making the machine more sensitive will correct this problem. The patient's inspiratory effort should result in an immediate flow of gas. The usual sensitivity setting for a pressure-triggered breath is –1 to –2 cm H_2O. It should be noted that if the inspiratory flow is inadequate, the patient may generate a large negative inspiratory effort and continue pulling as the breath is being delivered. This will make the pressure

by mansdocs.com

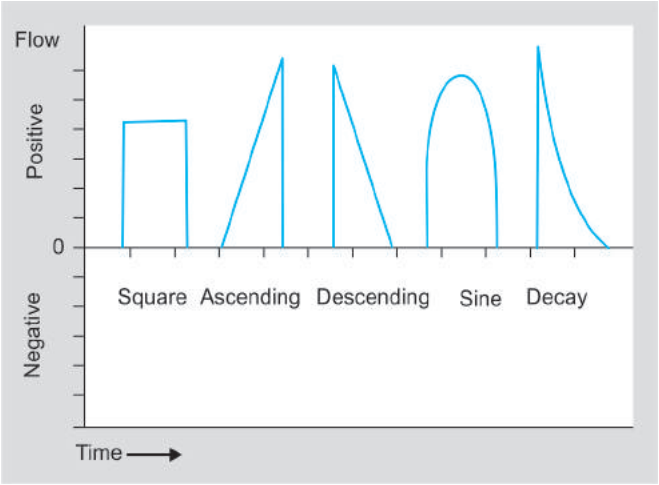


Fig. 2: Flow patterns of ventilatory flow patterns.

waveform look irregular and nonlinear as the breath is given, so increasing the flow will correct this.

If the pressure-time waveform shows a breath-triggering problem not related to sensitivity, the intensivist should consider checking the gas source, the driving pressure, and the machine calibration.

Flow-Time Waveforms

Flow delivery can be set as square (rectangular), ascending ramp, descending ramp, sine (sinusoidal), or decay (exponential) (Fig. 2). Most ventilators usually give a choice of two or three of these, but this depends on the mode of ventilation, since some flow patterns are preset due to the characteristics of the breath delivery. For example, volume controlled ventilation (VCV) may have several choices of flow patterns, including square, ascending ramp, descending ramp, and sine wave, while pressure controlled ventilation (PCV) uses a descending ramp or decelerating flow pattern.

WAVEFORMS IN DIFFERENT MODES OF VENTILATION

Figures 3A and B show a side-by-side comparison of the pressure-time, volume-time, flow-time waveforms in PCV versus VCV over four breaths. Both examples show that the ventilator settings include 10 cm H_2O of Positive end expiratory pressure (PEEP), shown by the baseline tracing at +10 on the pressure-time waveforms. On both tracings, the first and last breaths are mandatory, the first breath is time triggered, and the last three breaths are patient triggered (as seen in the triggering deflection on the pressure-time waveform). Pressure support of 20 cm H_2O is being delivered during the two spontaneous (second and third) breaths.

When examining pressure-time waveforms for either VCV or PCV with the addition of PEEP, clinicians should notice the baseline pressure between breaths should be fairly flat. If the baseline pressure drifts downward, it may indicate a leak in the system (at the exhalation valve, at a connection in the ventilator circuit, or around the endotracheal tube). The baseline may show slight movement up and down due to the heartbeat (cardiac oscillation). A difference between delivered tidal volume and measured exhaled tidal volume or a variation in the volume-time waveforms comparing similar types of breaths (two mandatory, time-triggered breaths) may also point to a leak in the system.

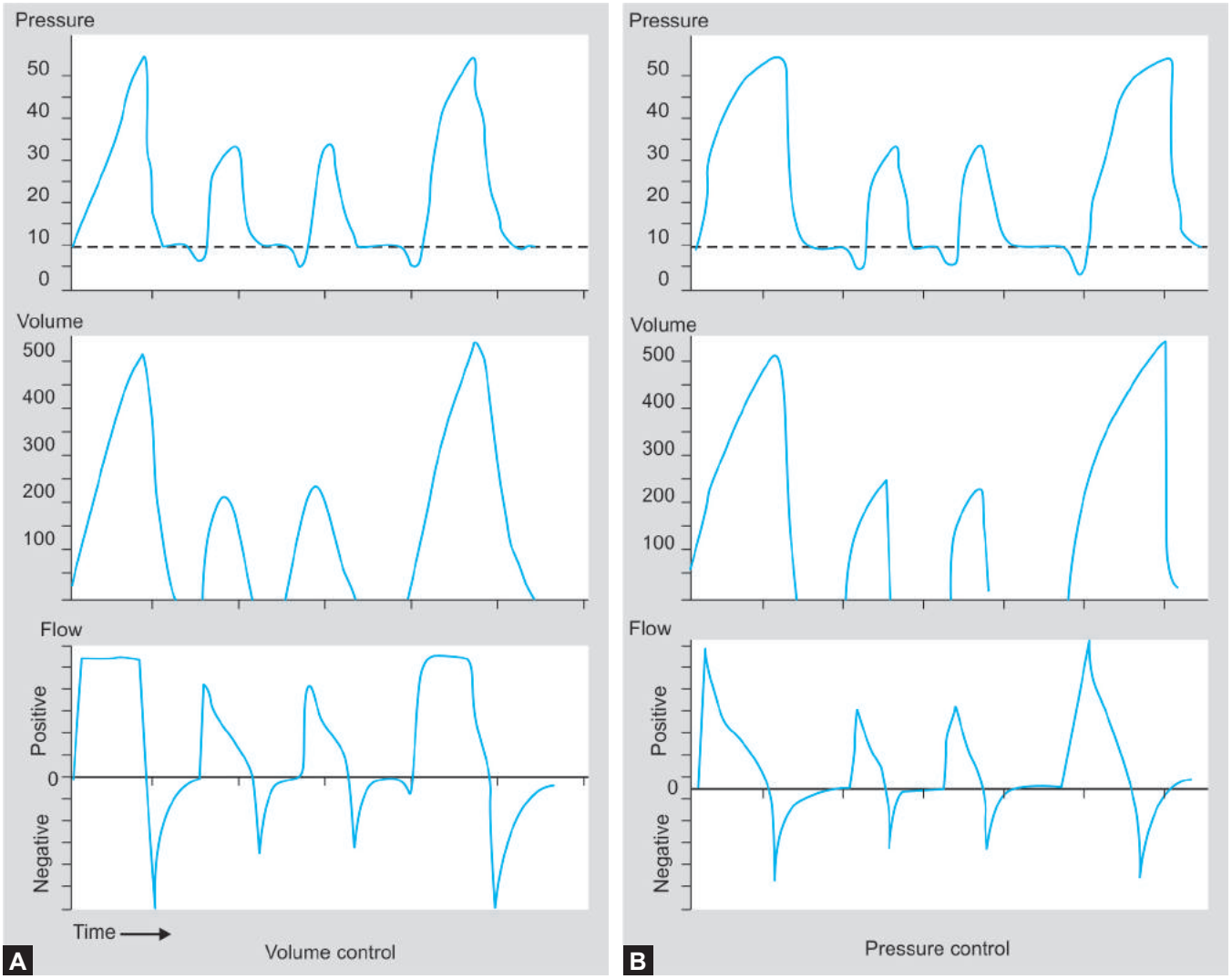
Finding AutoPEEP with Graphics

AutoPEEP (also called intrinsic PEEP) and air trapping can be uncovered by carefully examining the waveforms. AutoPEEP occurs when inspiration starts before the end of the previous breath (before a completion of exhalation and often happens in patients with high respiratory rates or high minute volumes, or when PEEP settings are higher. The volume-time and flow-time waveforms show this problem during the expiratory phase of the breath, as shown in Figure 4. At the end of exhalation, the volume-time waveform approaches the baseline then starts upward immediately with the next breath. Conversely, at the end of exhalation on the flow-time curve, there is an abrupt movement up to the baseline and an immediate starting of inspiratory flow for the next breath.

Understanding Ventilator Loops

Loops allow us to analyze the inspiratory and expiratory phases of each breath using either flow-volume or pressure-volume (PV) tracings. On the flow-volume loop, volume is plotted on the X-axis and flow on the Y-axis. Positive flow from a positive-pressure breath often appears above the horizontal axis, with expiratory flow below the axis, but this pattern may be reversed, depending on the ventilator being used. In the examples given here, positive flow from the ventilator (during inspiration) will be above the horizontal axis and negative flow (during exhalation) will be below the axis. On most PV loops, the pressure is plotted on the X-axis; volume, on the Y-axis. Patient-triggered breaths will look different from time-triggered or machine-triggered breaths on the PV loops, as the

by mansdocs.com



Figs. 3A and B: Volume-controlled ventilation vs pressure-controlled ventilation over four breaths.

patient generates a negative pressure at the beginning of inspiration.

Figure 5 shows a patient-triggered breath and the resulting PV loop that traces the inspiration and exhalation.

Figure 6 shows a decelerating-ramp flow pattern on a flow-volume loop. It shows the rapid increase in flow of early inspiration reaching peak flow, then decreasing to the end of inspiration and reaching zero flow. There is no time factor in these tracings, and exhalation follows immediately after the inspiratory phase on each of these loops.

The Inflection Points Using Loops

The PV loop can be used to evaluate PEEP and peak inspiratory pressure (or mandatory tidal volume) settings. A point can be determined, early in the inspiratory phase, at which there is a change in the slope of the line that shows a more rapid increase in volume per unit of pressure. This is the *lower inflection point (LIP)*. In the pattern of a typical PV loop on inspiration (without PEEP), the LIP is thought to show the point at which alveoli begin to fill rapidly and alveolar recruitment begins. Setting the PEEP level just above LIP is recommended.

At the other end of the inspiratory tracing on the PV loop, overdistension from higher inspiratory volume will show up as a bird-like beak as the lung's maximum volume is reached due to continued inspiratory flow. The point at which this line begins to flatten and form the beak is the *upper inflection point (UIP)*.

by mansdocs.com

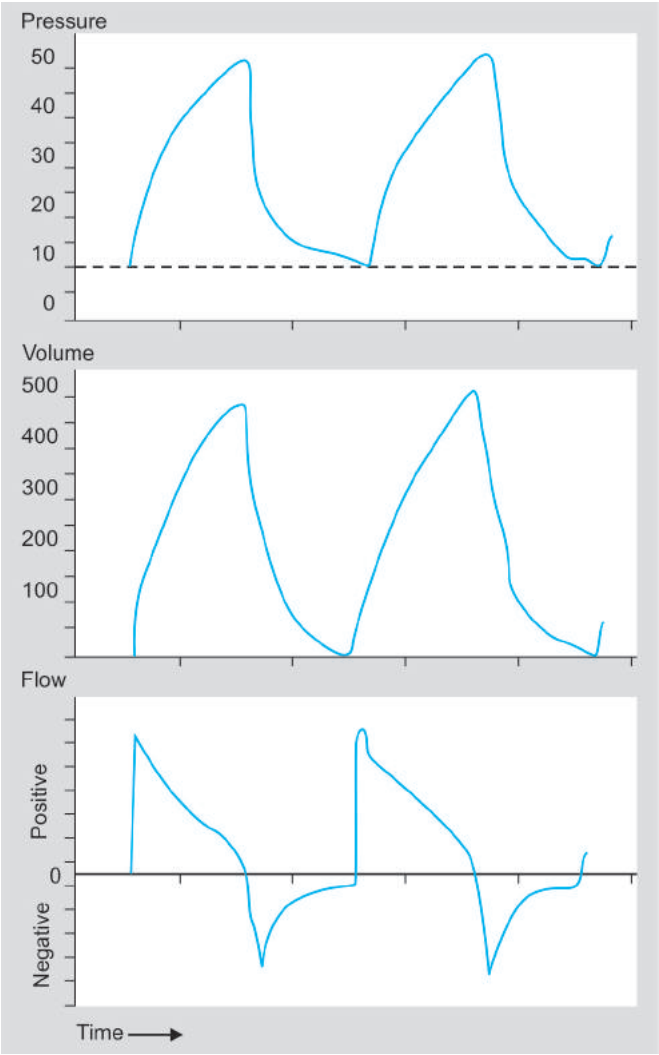


Fig. 4: Volume-time and flow-time waveforms during the expiratory phase of the breath. Flow-time suggests presence of AutoPEEP.

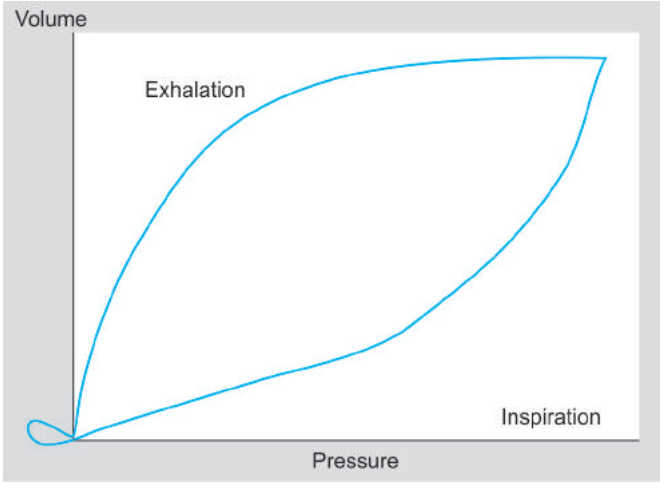


Fig. 5: Patient-triggered breath pressure-volume loop.

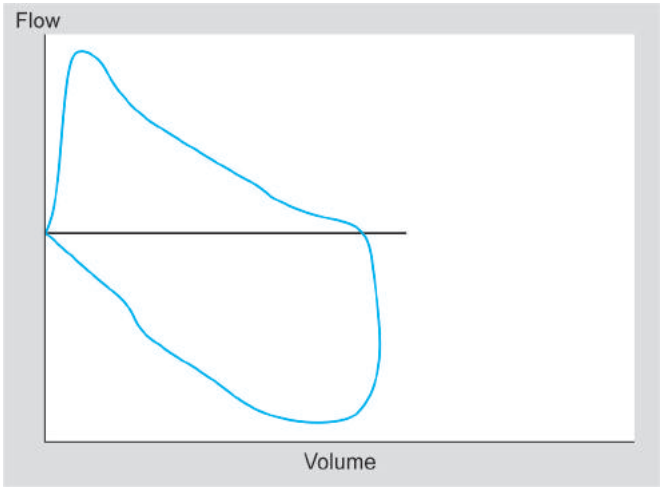


Fig. 6: Decelerating-ramp flow pattern on a flow-volume loop.

Figure 7 shows the LIP (with tracings showing how this changes with increasing flow) and the UIP for a delivered volume that is at the maximum setting (overdistension would begin to show up if delivered volume were increased).

Figure 8 shows the beak representing overdistension as too much volume is delivered. In this situation, the volume needs to be reduced to avoid the problems related to overdistension (barotrauma, volutrauma, decreased venous return, and decreased cardiac output).

Abnormal PV Loops in Clinical Practice

Some of the commonly seen abnormalities in PV loops showing PEEP (Fig. 9), airway resistance change (Fig. 10), overdistension (Fig. 11), leakage (Fig. 12), rate and flow asymmetry (Figs. 13 and 14), and compliance changes (Figs. 15A to C) are given.

CONCLUSION

Patient comfort and the effectiveness of mechanical ventilation can be significantly improved using the information provided by the ventilator graphics monitor. Ventilator graphics thus constitute a valuable tool, and a thorough understanding of the associated patterns, problems, and corrections will help us to provide high-quality, effective care.

by mansdocs.com

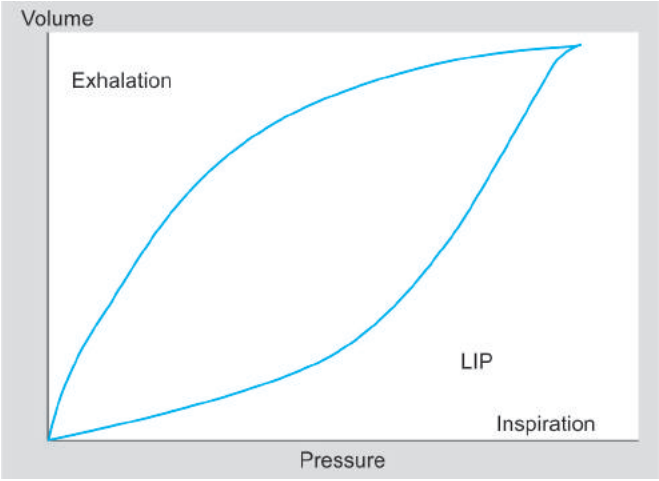


Fig. 7: Lower inflection point (LIP) and upper inflection point (UIP).

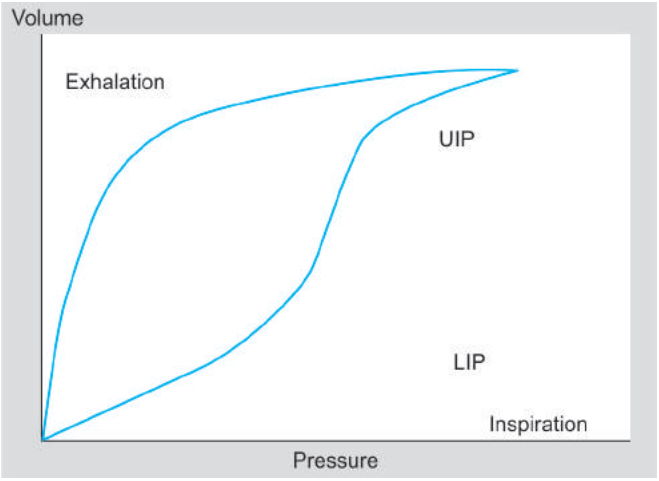


Fig. 8: The beak represents overdistension as too much volume is delivered.

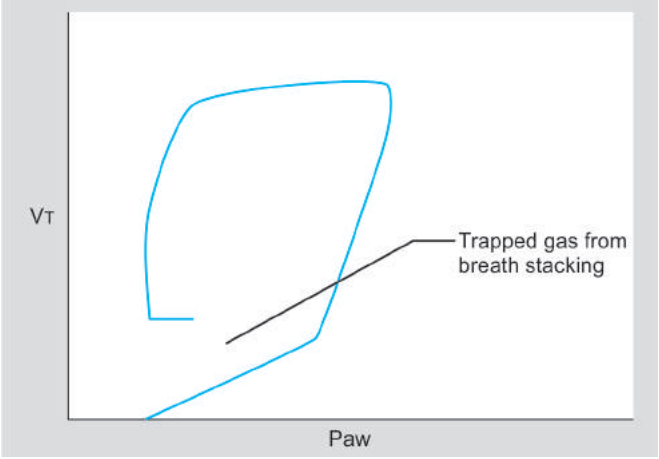


Fig. 9: Air trapping (AutoPEEP).

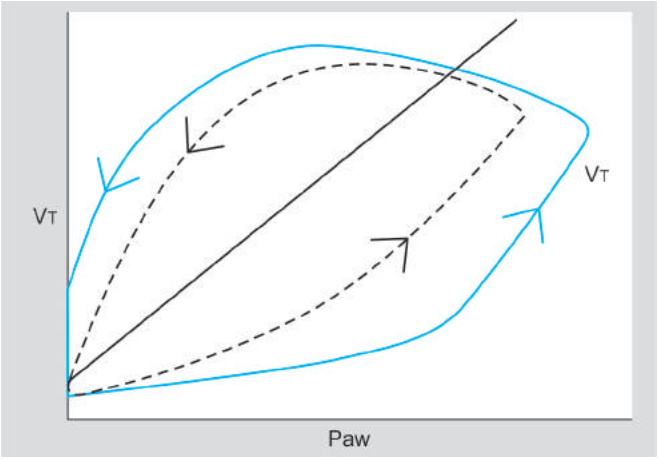


Fig. 10: Airway resistance changes (dashed line is normal).



Fig. 11: Overdistention of lung (beaking).

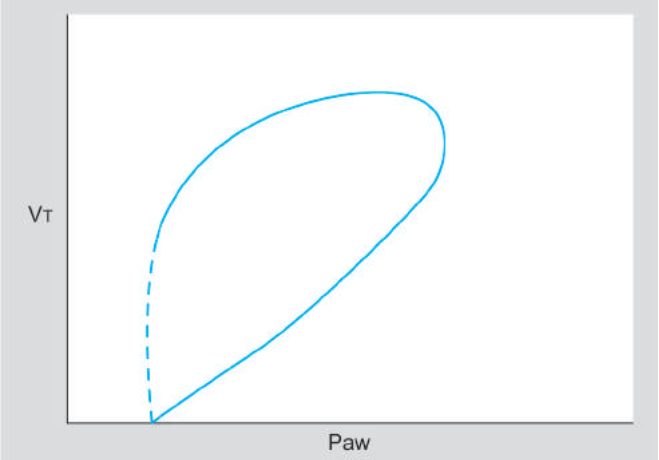


Fig. 12: Leakage.

by mansdocs.com

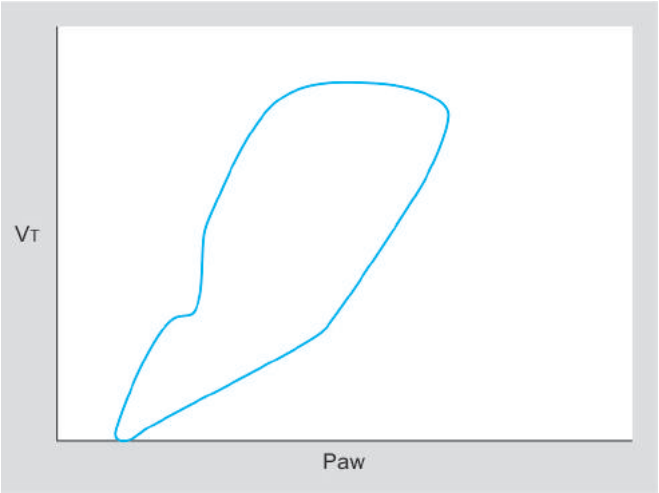


Fig. 13: Rate (Cycle) asynchrony.

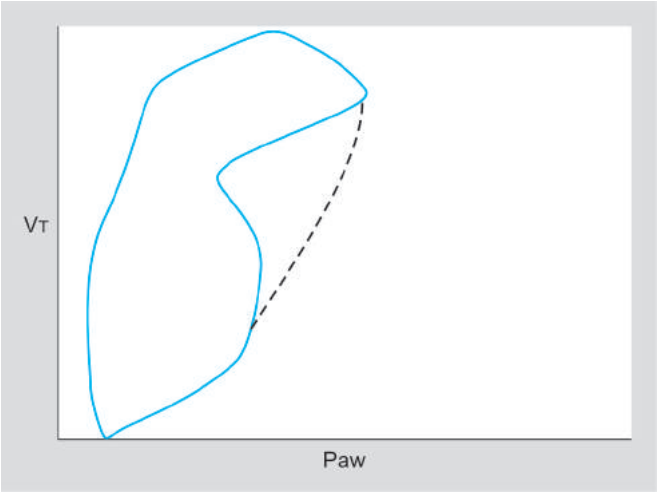
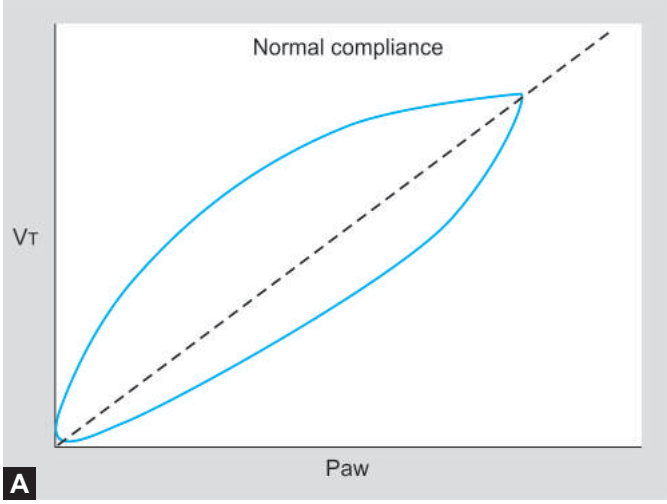
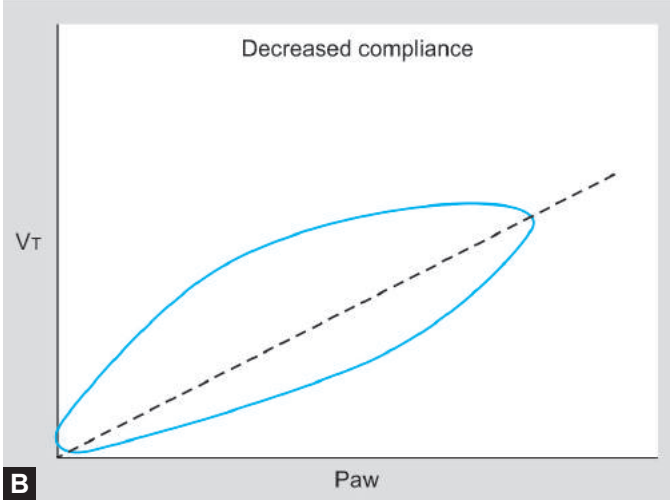


Fig. 14: Flow asynchrony (Flow starvation).







Figs. 15A to C: Compliance changes.

by mansdocs.com

BIBLIOGRAPHY

1. Branson R, Hess D, Chatburn R. Respiratory Care Equipment, 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 1999.
2. Haas C. Volume-pressure curves during mechanical ventilation. AARC Times. 2000;24:64-8.
3. In: Ouellet P (Ed). Waveform and Loop Analysis in Mechanical Ventilation. Solna, Sweden: Siemens-Elema; 1997.
4. In: Pilbeam S (Ed). Mechanical Ventilation: Physiological and Clinical Applications, 2nd edition. St Louis: Mosby; 1998.
5. In: Scanlon C, Wilkins R, Stoller J (Eds). Egan's Fundamentals of Respiratory Care, 7th edition. St Louis: Mosby; 1999.

by mansdocs.com

CHAPTER

74

Newer Modes of Ventilation

Rajesh Pande, Vipin Kauts

INTRODUCTION

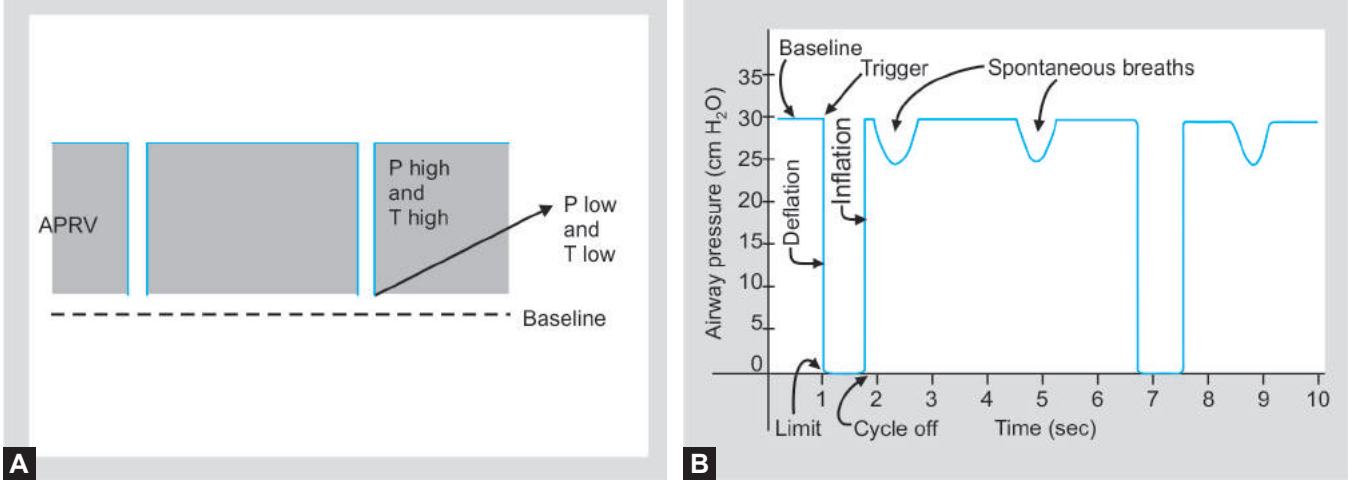
Airway pressure release ventilation (APRV) and bi-level positive airway pressure (BPAP) are variants of inspiratory reserve volume (IRV) in patients with acute respiratory failure (ARF) who are breathing spontaneously. These provide added ventilatory support to a patient who needs high levels of continuous positive airway pressure (CPAP) for oxygenation, but can provide most of the ventilatory power requirements without machine assistance.

Both allow ventilatory efforts to occur around an elevated baseline pressure (P high) over a set time (T high), but also depressurize the system partially or completely for brief periods (T low) at a frequency set by the physician. BPAP can provide entire range of ventilatory support (from controlled to unsupported breathing) (Figs. 1A and B).

AIRWAY PRESSURE RELEASE VENTILATION

Airway pressure release ventilation is an extreme form of bi-level ventilation, where long period of high pressure is followed by a very short period of low pressure (release) resulting in a high inverse ratio 8–9:1.

It is time-triggered, pressure-limited and time-cycled mode. Patient is ventilated on the expiratory limb of the pressure-volume (PV) loop.



Figs. 1A and B: (A) Airway pressure release ventilation: P high/T high and P zero/T low (0.6–0.8 sec); (B) Airway pressure release ventilation–allowing spontaneous breathing.

by mansdocs.com

- *Expiratory time (Te) is the key variable*:
  - Should be short enough to prevent derecruitment.
  - Should be long enough to get suitable tidal volume (TV).
  - Expiratory time is set- 0.4–0.6 sec (targeting TV 4–6 mL/kg)
    - If volume is inadequate, expiratory time is lengthened.
    - If volume is more, expiratory time is shortened.
  - *High pressure (P high) (CPAP)*: Set as mean airway pressure from previous modes [conventional mechanical ventilation (CMV), pressure controlled ventilation (PCV)] or empirically start with 28; then come down.
  - *Low pressure (P low)*: Set at zero. Acts as a release. Large pressure ramp allows for TV in a very short expiratory time.
  - *Inspiratory time (Ti)*: 4–6 sec (Respiratory rate should be 8–12 and not more).

Logic for very short optimal release time (t = C x R): It is time taken for emptying of 63% of lung volume. C is compliance of lung and chest wall. R is the resistance of airways and the ET tube. When compliance is small [acute respiratory distress syndrome (ARDS)], "t" is shorter. A practical equilibrium point corresponds to four time constants. The short release time creates an intentional auto-positive end expiratory pressure (PEEP) (time it takes for lung volume in expiratory state to reach a steady state no expiratory flow) equal to four time constants. Since release time is short, it creates intentional auto-PEEP. Since the release time in APRV is much shorter than the equilibrium time, a residual volume of air remains in the lung, creating intentional auto-PEEP. Since it is auto-PEEP, it allows us to use low pressure of zero, without any derecruitment. Ideally, this intentional auto-PEEP should be high enough to avoid derecruitment (optimally above the lower inflection point). In APRV, the auto-PEEP is controlled by the settings, and this intentional restriction of the expiratory flow is critical to avoid derecruitment of unstable alveolar units.

T high: Time spent at high pressure—80–95% of the cycle. (Lungs are inflated 80–95% of the time).

T low: 0.6–0.8 sec.

In APRV, the alveoli are mostly in inspiratory phase (recruitment) and are ventilated at the mean airway pressure, maximizing oxygenation, besides preventing collapse of unstable alveoli and recruitment of additional alveolar units in the injured lung due to significantly increased inspiratory time.

Application of Airway Pressure Release Ventilation

Check plateau pressure in PCV/volume controlled ventilation (VCV) modes. If less than 30 cm H_2O, use it as high pressure. If more than 30 cm H_2O, choose 30 cm H_2O as high pressure.

Set P low as zero.
T high = 4 sec
Start T low with 0.6-0.8 sec.

Adjustments

- *Hypoxia*: Adjust MAP (P high and T high) and FIO_2. May require one or both changes.
- Alveolar ventilation
- Increase pressure gradient (P high–P low)
- Increase/adjust airway pressure release time (T low)
- Airway release frequency (=60/cycle time)
- T low is adjusted according to flow time curve, so that the pressure release ends when expiratory flow reaches 40% of the peak expiratory flow. i.e. approximately one time constant
- *Hypercarbia*: Some degree is acceptable.

High Mean Airway Pressure

Lung ventilation in mean airway pressure (pressure averaged over the entire respiratory cycle) offers the advantages of lung recruitment and better oxygenation. However, due to long inspiratory time, there could be disadvantages like worsening of air leaks, increase in right ventricular (RV) afterload, worsening of pulmonary hypertension, decreased venous return and cardiac outout, and indirect lung injury. However, spontaneous breathing in this mode promotes dependent area ventilation, better venous return, high glomerular filtration rate (GFR), better small bowel perfusion and lower sedation requirements.

Mean airway pressure: Averaged over the entire respiratory cycle time (inspiration and exhalation).

Advantages: Lung recruitment, better oxygenation.

Disadvantages: Worsening of air leaks, increase in RV afterload, worsening of pulmonary hypertension, decreased RV return, decreased cardiac output, indirect lung injury.

Spontaneous breathing: Promotes dependent areas ventilation, better venous return, high GFR, better small bowel perfusion, lower sedation requirement.

by mansdocs.com

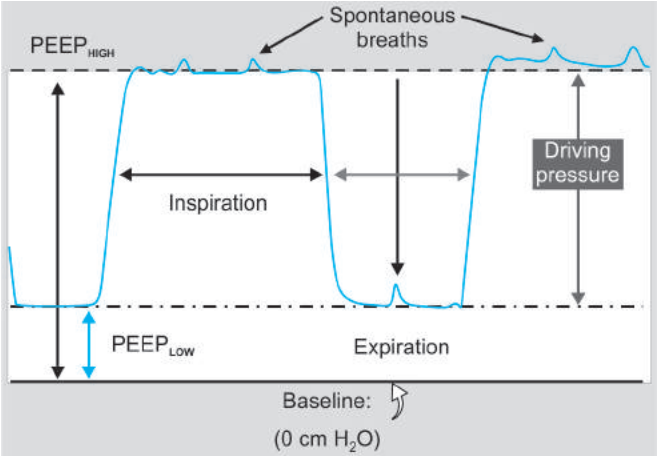


Fig. 2: Bi-level mode.

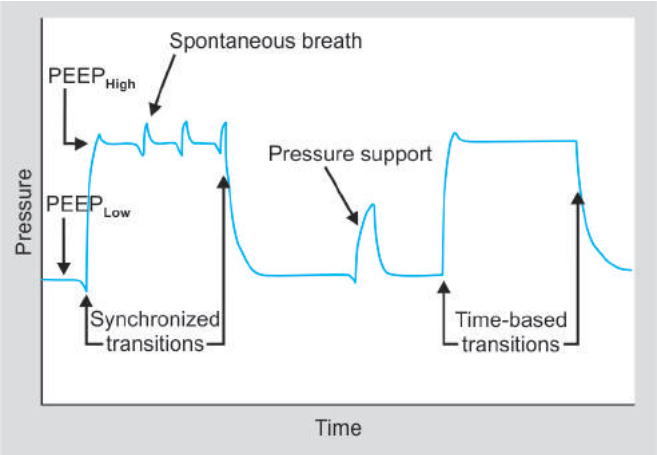


Fig. 3: Bi-level mode with pressure support.

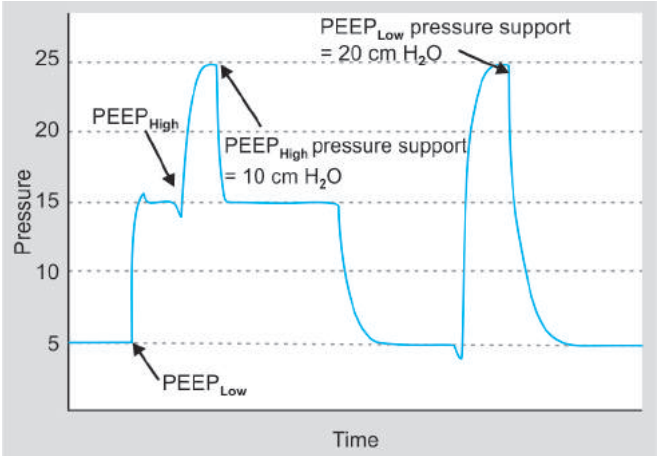


Fig. 4: Bi-level with pressure support.

Bi-level Mode

Bi-level is a mixed mode that combines the attributes of mandatory and spontaneous breathing and is classified as a mixed mode. Here, the mandatory breaths are pressure controlled and the spontaneous breaths are pressure supported (Figs 2 and 3).

Bi-level ventilation is essentially two levels of continuous positive airway pressure—PEEP High and PEEP Low. The difference between PEEP high and PEEP low serves as the driving force for ventilation. Cycling between the mandatory and spontaneous modes can be triggered by bi-level timing settings or by patient's spontaneous breathing effort. The difference between PEEP high and PEEP low can be adjusted to deliver a tidal volume of 6–8 cm^3/kg in accordance with the ARDSnet guidelines.

Inspiratory and expiratory times can be manipulated as well enabling inverse ratio ventilation in which short expiratory times enable ventilation and longer inspiratory times encourage recruitment of alveoli, thus facilitating oxygenation (APRV).

Using Pressure Support with Bi-level Mode of Ventilation

Spontaneous breaths in bi-level mode can be assisted by pressure support both at PEEP low and PEEP high (Fig. 4). At PEEP low, the pressure support is always set relative to PEEP low. Target pressure is PEEP low + pressure support. At PEEP high, the spontaneous breaths at PEEP high are not supported by pressure support, unless pressure support is more than (PEEP high-PEEP low). For example: PEEP low = 5 cm H_2O, PEEP high = 15 cm H_2O, pressure support = 20 cm H_2O. All spontaneous breaths at PEEP low are supported by 20 cm H_2O. Total pressure remains 25 cm H_2O. All spontaneous breaths at PEEP high are supported by 10 cm H_2O [Pressure Support - (PEEP high – PEEP low)]; total pressure remains 25 cm H_2O.

Automatic Tube Compensation

Automatic tube compensation (ATC) for ET tube resistance works by using a closed loop control of tracheal pressure. It is similar to pressure-support ventilation (PSV) but the pressure applied by the ventilator varies as a function of the ET tube resistance and flow demand. ATC added to PSV may increase the tidal volume substantially.

Advantages:

- To overcome work of breathing (WOB) imposed by artificial airway.
- To improve patient ventilator synchrony by varying flow commensurate with demand.
- Reduce air trapping by compensating for imposed expiratory resistance.

by mansdocs.com

PROPORTIONAL ASSIST VENTILATION

Proportional assist ventilation (PAV) works based on the concept of equation of motion, which states that the pressure applied by the respiratory muscle (Pmus) to the system is to overcome the elastic (elastance, E) and resistive (resistance, R) opposing forces.

Pmus = Pres + Pelas.

Elastance is proportional to the volume (V) displacement, whereas resistance is proportional to the airflow rate (V') neglecting inertia:

Pmus = E × V + R × V'

It provides ventilatory assistance in terms of flow assist (FA, cm H_2O/L/s) and volume assist (VA, cm H_2O/L), which can specifically unload the resistive and elastic burdens respectively. In clinical practice, both FA and VA are usually applied at the same time for effective ventilatory support.

The pressure applied to inflate the respiratory system is a result of combination of patient's inspiratory effort and the positive pressure applied by the ventilator to the airway opening, depending on the levels of FA and VA, set by the clinician:

Pmus = V × (E – VA) + V' × (R – FA).

Proportional assist ventilation uses the compliance and resistance information collected every 4–10 breaths to know what it is fighting against. It also uses the flow and volume information collected every 5 milliseconds to know what the patient wants. PAV combines this data with the percent support information input by the clinician to determine how much pressure is needed to support the system.

Practically, PAV is intended for use in spontaneously breathing patients with ideal body weight more than 25 kg, with either endotracheal or tracheostomy tubes of internal diameter 6–10 mm. Patients must also have satisfactory neural-ventilatory coupling, and stable, sustainable inspiratory drive (if patient does not have inspiratory effort, there is no volume/flow support in the PAV mode).

The potential advantages are patient comfort, lower peak airway pressures, decreased sedation or paralysis requirement, less likelihood of overventilation, preservation and enhancement of patient's own control mechanisms such as metabolic arterial blood gas (ABG) control and Hering-Breuer reflex and improved efficiency of negative pressure ventilation.

The limitation to the use of this technique is significant circuit leak and it is not recommended to be used with noninvasive ventilation (NIV). A jet nebulizer that uses external flow cannot be used with PAV.

Proportional assist ventilation is intended for invasive positive pressure ventilation (IPPV) use; its application in noninvasive positive pressure ventilation (NIPPV) has also been examined.

As for any other positive feedback regulation system, one major inherited problem in its NIPPV use is volume/flow overassistance/overventilation called "runaway phenomenon", which occurs when pressure provided at the end of inspiration exceeds opposing elastic and resistive pressures of the patient. It is especially when there is moderate interface leak for which ventilator cannot distinguish air flow to patient or to interface (leak). Continuation of positive pressure after the end of patient's inspiratory effort into the neural expiration results in patient-ventilator asynchrony and discomfort.

Other conditions that predispose runaway include:

- Errors in estimation of elastance and/or resistance (machine measurement error),
- Inappropriate high setting of FA or VA (clinician error) and
- Improvement in E/R properties of respiratory system (i.e. improved respiratory mechanics after effective therapy in obstructive airway diseases).

Nevertheless, runaway is a rather benign condition. It can be aborted by expiratory effort [or even natural stiffening of respiratory system near total lung capacity (TLC)] of the patients or purposefully by safety alarms of the ventilator machine which limit excessive airway pressure/delivered tidal volume/inspiratory time.

NEURALLY ADJUSTED VENTILATORY ASSIST

Neurally adjusted ventilatory assist (NAVA) is an assist mode of mechanical ventilation that delivers a pressure proportional to the integral of the electrical activity of the diaphragm (Edi) It is based on neural respiratory output. The Edi is captured, fed to the ventilator and used to assist the patient's breathing in synchrony with the ventilator. As the work of the ventilator and the diaphragm is controlled by the same signal, good coupling occurs between the diaphragm and the ventilator.

Neurally adjusted ventilatory assist is available for both invasive and NIV, assuring effective patient-ventilator synchrony independent of patient interface. The brain's respiratory center sends a signal, which travels via the

by mansdocs.com

phrenic nerve and excites the diaphragm. The Edi catheter captures the electrical activity of the diaphragm. The ventilator uses the Edi signal to synchronize ventilation to the patient's breathing efforts.

The Edi signal can be used as a diagnostic tool to monitor the Edi in any situation or ventilation mode as well as in standby after extubation. This provides useful information on respiratory drive, volume requirements and the effect of the ventilatory settings.

An increasing Edi may signify increasing weakness or worsening of the patient's condition, as objective criteria for intubation decisions. As the patient's condition improves, the decreasing Edi amplitude and pressure drop are an indicator to consider weaning and extubation. The Edi signal enables clinicians to set the assist level from the ventilator and to optimize unloading. PEEP titrated to the lowest Edi means that WOB is minimized. As the patient's condition improves with NAVA, Edi amplitude decreases resulting in a reduction in ventilator-delivered pressure.

Neurally adjusted ventilatory assist provides patient comfort as the respiratory muscles and the ventilator are driven by the same signal. This synchrony minimizes patient discomfort and agitation, promotes spontaneous breathing, and provides for improved sleep quality and possibly reduced sedation. It decreases patient's pressure load and avoids overassist. The use of NAVA helps avoid overassistance or underassistance of the patient.

In clinical studies, NAVA has been associated with lower levels of peak airway pressures compared to conventional mechanical ventilation with pressure support.

Steps to initiate NAVA:

- Verify Edi catheter position
- Connect the Edi catheter to the Edi cable
- Open the "Neural access" menu
- Select "Edi catheter positioning"
- Adjust catheter position by looking for a diminishing electrocardiograph (ECG) waveform progression from the first to the fourth waveform and the presence of blue color in the second and third waveforms.
- Set the initial NAVA level
- Press the neural access button and select NAVA preview
- Press the NAVA level button and adjust the main rotary dial so that the gray superimposed curve (Pest = pressure estimate) approximates the yellow pressure tracing
- Accept by pushing the main rotary dial and press "close" to save the NAVA level
- *Note*: The Edi peak goal is 5–15 and Edi minimum is usually less than three. Be aware that Edi fluctuates breath to breath.

If the response to an increase in NAVA does not result in a reduction in Edi, the ventilator increases the delivered pressure. However, a reflexive or involuntary reduction in Edi would mitigate the effects of an increased NAVA level, and the delivered pressure may remain unchanged or be less than anticipated. Thus, the response in Edi to an increase in the NAVA level determines the resulting transpulmonary pressure (Ptp) whether volume changes or not.

The long-term reliability of NAVA in critically ill patients is largely unknown. Patients with unstable or unreliable ventilatory drives (e.g. patients with fluctuating sedation/analgesia needs) are at risk for suboptimal ventilatory support. It is not clear which patient will really benefit from the improved synchrony in NAVA as the technique is quite expensive and complex.

BIBLIOGRAPHY

1. Cairo JM (ed), Pilbeam's Mechanical Ventilation: Physiological and Cinical Applications. 5th ed, 2012, Elsevier.
2. Chang DW. Clinical application of mechanical ventilation. 3rd ed, 2006, Delmar Cengage Learning.
3. Frawely PM, Habashi NM. Airway release pressure ventilation: Theory and practice. 2001;12:234-46.
4. Habashi NM. Other approaches to open lung ventilation. Airway pressure release ventilation. Crit Care Med 2005; 33S:S228-S240.
5. Mclntyre NR, Branson RD. Mechanical ventilation. 2nd ed, 2008, Saunders.

by mansdocs.com

CHAPTER

75

Weaning/Liberation from Mechanical Ventilation

Rajesh Pande, Monish Nakra

INTRODUCTION

Mechanical ventilation costs $2,000 per day in US. Six percent of ventilated patients require prolonged ventilation, but consume 37% of ICU resources. Time spent on weaning is 40–50% of the entire duration of mechanical ventilation. Unplanned extubations, 0.3–16%; in 83% cases, it is initiated by the patient, 17% being accidental. Mortality is 12% if there is no delay in extubation, but 27% when it is delayed. Mortality increases with increasing duration of ventilation: ventilator-associated pneumonia (VAP) and airway trauma. Weaning remains one of the most challenging problems in intensive care. Following discontinuation of mechanical ventilation, 25% of patients have severe respiratory distress requiring reinstitution of ventilatory support.

Premature extubation may lead to:

- Loss of airway protection (aspiration)
- Hypoxemia
- Sympathetic discharge—cardiovascular stress
- Muscular fatigue and acidosis
- Reintubation into an edematous airway (risk of hypoxic brain injury, etc).

Prolonged ventilation may result in:

- Nosocomial pneumonia
- Stretch injury and barotraumas
- Airway trauma
- Prolonged sedation
- Along with the obvious increase in costs associated with prolonged ventilation.

Weaning covers the entire process of liberating the patient from mechanical support and from the endotracheal tube, including relevant aspects of terminal care (Fig. 1).

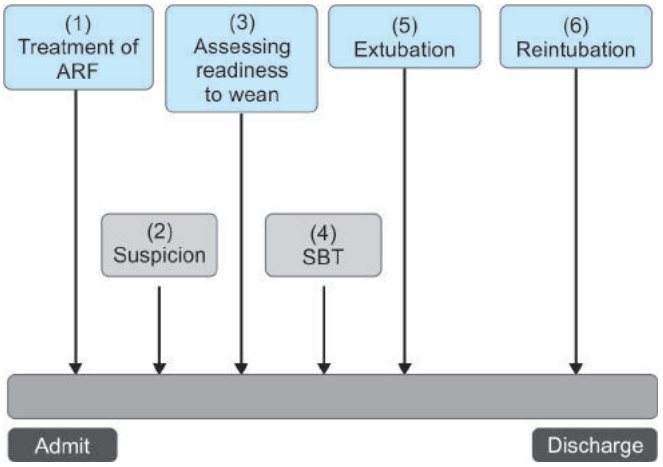


Fig. 1: Schematic representation of the different stages occurring in a mechanically ventilated patient.
(ARF: Acute respiratory failure; SBT: Spontaneous breathing test).

Treatment of acute respiratory failure: Period of care and resolution of disorder that caused respiratory failure and prompted the mechanical ventilation.

Suspicion: The point at which the clinician suspects that the patient may be ready to begin the weaning process.

Assessing readiness to wean: Daily testing of physiological measures of readiness of weaning [maximal inspiratory pressure (MIP), frequency to tidal volume ratio (f/VT)] to determine probability of weaning success.

Spontaneous beathing trial: Assessment of patient's ability to breathe.

Extubation: Removal of endotracheal tube.

Reintubation: Replacement of endotracheal tube for patients who are unable to sustain spontaneous ventilation.

by mansdocs.com

Weaning failure: Failure of spontaneous breathing trial (SBT) or the need for reintubation within 48 hours. Failure of SBT can be classified as per the objective and subjective criteria.

Simple weaning: Patient who proceed from initiation of weaning to successful extubation on the first attempt without difficulty.

Difficult weaning: Patients who fail initial weaning and require up to three SBTs or as long as 7 days from the first SBT to achieve successful weaning.

Prolonged weaning: Patients who fail at least three weaning attempts or require more than 7 days of weaning.

FACTORS AFFECTING WEANING

Respiratory Load

- *Clinical assessment:* Hemodynamically stable, awake, the disease process has been treated adequately
- *Indices of minimal ventilator dependency are present:* $FIO_2 \leq 0.5$, positive-end expiratory pressure (PEEP) ≤ 8 cm H_2O, $PaO_2/FIO_2 \geq 150$ mm Hg, arterial oxygen saturation (SaO_2) ≥ 90%.
- Success of weaning will depend on ability of respiratory muscle pump to tolerate work of breathing (WOB).
- Resistance < 5 cm $H_2O\ L^{-1}\ s^{-1}$
- Static compliance 0.06–0.1 L cm H_2O^{-1}
- A maximum inspiratory pressure value of ≤ – 20 to – 25 cm H_2O is associated with successful weaning.
- *Pmax:* Excellent negative predictive value if < – 20 (in one study 100% failure to wean at this value).
- An acceptable Pmax, however, has a poor positive predictive value (40% failure to wean in one study with a Pmax > – 20).
- Some predictors of successful weaning are listed in Table 1, although no single factor has been found to independently predict weaning success.

Cardiac Load

- Patients with ischemic heart disease, valvular heart disease, and systolic or diastolic dysfunction present before, or identified during critical illness.
- Patients with subtle and less easily recognized myocardial dysfunction are the difficult ones.
- Increased cardiac workload:
  - Dynamic hyperinflation
  - Increased serum lactate and low $ScVO_2$ are predictors of poor weaning.

Table 1: Predictors of weaning outcome.

Predictor	*Value*
Evaluation of ventilatory drive:	
• P 0.1	• <6 cm H_2O
Ventilatory muscle capability:	
• Vital capacity	• >10 mL/kg
• Maximum inspiratory pressure	• < – 30 cm H_2O
Ventilatory performance:	
• Minute ventilation	• <10 L/min
• Maximum voluntary ventilation	• >3 times V_E
• Rapid shallow breathing index	• <100
• Respiratory rate	• <30/min

- Unoptimized cardiovascular function:
  - Arrhythmias
  - Fluid overload
  - Myocardial contractility.

Neuromuscular Causes

- Decreased central drive
- Peripheral neuromuscular dysfunction
- Critical illness neuromuscular abnormalities (CINMA)
  - Neuromuscular transmission is normal.
  - Decreased motor action potentials and fibrillation potentials may resemble a motor axonopathy.
  - Improves over weeks, but some residual deficit may be there.

CNS Causes

- Delirium:
  - Modifiable risk factors:
    - Use of psychoactive drugs
    - Untreated pain
    - Sleep deprivation
    - Prolonged immobilization
    - Hypoxemia
    - Sepsis
    - Anemia
  - Prolonged ICU stay
  - Predictor of higher mortality up to 6 months after discharge.
- Anxiety and depression:
  - Contributors:
    - Dyspnea
    - Inability to communicate
    - Sleep fragmentation (patients are unable to rest or sleep)
  - Minimize anxiety:
    - Improvement in speech
    - Ventilating with bi-level pressure support ventilation (PSV)
    - Reducing noise when they sleep.

by mansdocs.com

- Daily sedation interruption or sedation vacation
- Boluses rather than infusions
- Dexmedetomidine:
  - Used in difficult weaning:
    - Beneficial in extubating agitated patients
    - Previous failed weaning attempts
    - Shorter extubation times
    - Fewer ventilator days
    - More successful extubation.

Function of Other Organs

- Body temperature:
  - 1° increases CO_2 production and O_2 consumption by 5%
- Normal electrolytes:
  - Potassium, magnesium, phosphate and calcium.
- Adequate nutritional status:
  - Under- or over-feeding
- Optimized renal, acid-base, liver and GI functions.

CONSIDERATIONS FOR ASSESSING READINESS TO WEAN

Clinical Assessment

- Adequate cough
- Absence of excessive tracheobronchial secretions
- Resolution of disease acute phase for which the patient was intubated.

Objective Measurement

Clinical Stability

- Stable cardiovascular status [heart rate (HR) ≤ 140 beat min^{-1}, systolic blood pressure (SBP) 90–160 mm Hg, no/minimum vasopressors]
- Stable metabolic status.

Adequate Oxygenation

- SaO_2 > 90% on FiO_2 ≤ 0.4 (or PaO_2/FiO_2 ≥ 150), PEEP ≤ 8 cm H_2O.

Adequate Pulmonary Function

- Frequency ≤ 35 breaths min^{-1}
- MIP ≤ – 20 to – 25 cm H_2O
- Tidal volume (VT) > 5 mL kg^{-1}
- Vital capacity (VC) > 10 mL kg^{-1}
- f/VT < 105 breaths min^{-1} L^{-1}
- No significant respiratory acidosis.

Adequate Mentation

- No sedation or adequate mentation on sedation (or stable neurological patient)
- Maximal inspiratory pressure: Pmax: Excellent negative predictive value if less than –20 (in one study 100% failure to wean at this value). An acceptable Pmax however has a poor positive predictive value (40% failure to wean in one study with a Pmax > –20).
- Rapid shallow breathing index (Yang, Tobin. RSBI. N Engl J Med. 1991;324:1445-50): It is determined during the first minute immediately after disconnection from ventilatory support while patients are still intubated and breathing spontaneously on room air. A threshold value of 105 bpm/l for the Rapid shallow breathing index (RSBI) can best discriminate between successful and failure weaning outcome.

When f/VT > 105, 95% weaning attempts were unsuccessful and when f/VT < 105, 80% were successful. It is one of the most predictive bedside parameters.

Failure Criteria of Spontaneous Breathing Trials

Clinical Assessment and Subjective Indices

- Agitation and anxiety
- Depressed mental status
- Diaphoresis
- Cyanosis
- Evidence of increasing effort
  - Increased accessories muscle activity
  - Facial signs of distress
  - Dyspnea.

Objective Measurement

- PaO_2 ≤ 50–60 mm Hg on FIO_2 ≥ 0.5 or SaO_2 < 90%
- $PaCO_2$ > 50 mm Hg or an increase in $PaCO_2$ > 8 mm Hg
- pH < 7.32 or a decrease in pH ≥ 0.07
- Rapid shallow breathing index [respiratory frequency to tidal volume (fR/VT)] > 105 breaths min^{-1} L^{-1}
- fR > 35 breaths min^{-1} or increased by ≥ 50%
- HR > 140 beats min^{-1} or increased by ≥ 20%
- SBP > 180 mm Hg or ≥ 20%
- SBP < 90 mm Hg
- Cardiac arrhythmias.

Spontaneous Breathing Trial

Trials of spontaneous breathing usually last 2 hours, but patients who fail usually show signs of poor

by mansdocs.com

tolerance earlier. A prospective, multicenter study in 526 ventilator-supported patients to compare trials of spontaneous breathing lasting 30 or 120 minutes. The percentage of patients who remained extubated for 48 hours did not differ between the two groups (75.9% vs 73.0%, $P = 0.43$). If the patient fails a spontaneous breathing trial, a 24 hour rest period should be provided before the next trial is undertaken.

T-tube or Pressure Support

Spontaneous breathing with a T-tube system may fail the test because they must work harder. Therefore, some investigators advocate PSV to counteract this extra work. The mean value of pressure support (PS) needed to compensate for the increased WOB caused by the ventilatory circuit and endotracheal tube was found to be 7 cm H_2O.

Studies have compared between the use of a T-tube vs PS (7 cm H_2O) in trials of spontaneous breathing in adult patients. Although, more patients in the T-tube group failed the trial (22% vs 14%, $P = 0.03$). There was no difference in percentage of patients who remained extubated after 48 hours (63% in the T-tube group vs 70% in PS group, $P = 0.14$).

TWO-STAGE APPROACH TO WEANING

- Systematic measurement of predictors, including f/VT, followed by a single daily trial of SBT was compared with conventional management in a randomized trial.
- Patients in single daily trial of SBT were weaned twice as rapidly. The rate of complications and the costs of intensive care were also lower with two-stage management than with conventional management.

ROLE OF NONINVASIVE VENTILATION IN WEANING

Noninvasive ventilation (NIV) offers the following advantages:

- Reduces mortality
- Reduces incidence of VAP
- Reduces ICU stay
- Reduces hospital stay
- Reduces time on endotracheal mechanical ventilation (ETMV)
- Reduction in proportion of weaning failure.

It has a good role in the following situations:

- Extubation in chronic obstructive pulmonary disease (COPD) patients
- Postextubation respiratory failure
- Weaning patients off the ventilator (failing T tube trial but otherwise fit for extubation).

Noninvasive ventilation may be used to expedite weaning in uncomplicated patients of COPD who fail an SBT (promising but evidence insufficient). NIV for reducing reintubation rate for postextubation failure is not recommended except in patients of COPD. Routine NIV application postextubation to preempt respiratory failure is not recommended.

APPLICATIONS OF NONINVASIVE VENTILATION

- This approach to weaning should be applied in a highly monitored environment
- When patient fails SBT, first stabilize him with full support for at least 1 hour.
- Then extubate patient to NIV
- Initially, apply NIV continuously
- Monitor closely
- Gradually, reduce time on NIV
- For COPD patients, who develop postextubation failure, use NIV if there are no contraindications and the patient is compliant.

SUMMARY

The prerequisite for weaning is reversal of the indication of mechanical ventilation. The readiness for weaning should be checked based on subjective and objective criteria. RSBI and maximum inspiratory pressure are good predictors of weaning. Patients should be given 30 minutes to 2 hours SBT, and ventilatory discontinuation should be done if patient tolerates SBT for 30–120 minutes.

Patient who fails an SBT should receive a stable, nonfatiguing, comfortable form of ventilatory support. There may be substantial benefits to early extubation and institution of noninvasive positive pressure ventilation. The use of liberation and weaning protocol facilitates the process and decreases the ventilator length of stay. Tracheostomy should be considered in situations of prolonged ventilatory failure.

BIBLIOGRAPHY

1. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335: 1864-9

by mansdocs.com

CHAPTER

76

Non-Invasive Ventilation

Rajesh Pande, Rakesh Gupta

INTRODUCTION

Non-invasive ventilation (NIV) is a way of delivering support to the patient's breathing *without* the use of a breathing tube (endotracheal tube). Extra support can be delivered by a mechanical ventilator, or by a special machine specifically designed for this type of therapy.

Non-invasive ventilation consists of mechanical breaths delivered by a tightly fitting nasal or facial mask or a helmet instead of an artificial airway, such as an endotracheal or tracheostomy tube. It relies on the patient being awake and able to breathe spontaneously. When they take a breath in, the NIV machine delivers positive pressure and supports that breath. It also prevents that breath from exhaling completely. All these techniques will make it easier to breath. NIV may also be achieved by the application of a negative-pressure generator to the chest ("chest box" or cuirass) or body ("iron lung") but not without major limitations.

It can be used short term and long term. Short-term use is usually for those patients who are experiencing an acute episode of breathing difficulties, and is usually administered over a period of days. Long-term use is for specific disease processes such as patients with obstructive sleep apnea and neuromuscular disease. These types of patients will probably use it for the rest of their lives.

Non-invasive ventilation usage in the intensive care unit (ICU) is increasing because of desire to avoid complications associated with invasive ventilation like:

- Use of sedation, ventilator-induced lung injury or ventilator-associated pneumonia, patient discomfort and need of sedation.

ADVANTAGES OF NIV

- The advantages of NIPPV over invasive ventilation are that it preserves normal physiologic functions such as coughing, swallowing, feeding and speech.
- Physiological warming and humidification occurs therefore reduces risk of ventilator associated pneumonia as well as tracheal and laryngeal injuries.
- Non-invasive ventilation is less expensive, and intensive care bed not necessarily required.
- It allows intermittent use, which facilitates weaning when used in acute settings.

Continuous positive airway pressure (CPAP) is a form of NIV that provides respiratory support even though the pressure applied is constant throughout the respiratory cycle. This mode provide ventilator support by alveolar recruitment leading to reduction in elastic work as well as reducing threshold load created in the presence of positive end expiratory pressure (PEEP), it also reduces LV transmural pressure (afterload). Bi-level positive airway pressure (BiPAP) allows separate settings for inspiratory and expiratory airway pressure levels, and is conceptually similar to pressure support ventilation (PSV) plus CPAP. Respiratory frequency is usually determined by the spontaneous rate but may be time-cycled and independent of patient effort.

DIFFERENT TYPES

Different types of interfaces are available:

- Full-face masks (70%)
- Nasal masks (25%)
- Nasal pillows or plugs (5%)

by mansdocs.com

- Mouthpieces and
- Custom fabricated masks
- Helmet that cover the whole head and all or part of the neck.

HOW DOES NIV WORK?

The respiratory effort (pressure-volume work) required to achieve a desired minute volume (VE) may be viewed as the summation of the individual forces that must be overcome to generate inspiratory flow, namely: elastic (P_{el}) work, flow-resistive (P_{res}) work (airflow obstruction), and threshold (P_{thres}). Since the volume component is constant the equation of motion can be written as:

$$P_{mus} = P_{el} + P_{res} + P_{thres}$$

With the addition of a device for ventilatory support, the respiratory muscle effort (P_{mus}) required by the patient is equivalent to the difference between the applied pressure at airway (P_{ao}) and the total work required to maintain VE.

$$P_{mus} = P_{el} + P_{res} + P_{thres} - P_{ao}$$

Or

$$P_{mus} + P_{ao} = P_{el} + P_{res} + P_{thres}$$

P_{thres} is the sum of intrinsic and extrinsic PEEP ($PEEP_i$). $PEEP_i$ is absent in the healthy lung, but common in the presence of tachypnea, airflow obstruction and dynamic hyperinflation. This threshold load must be counterbalanced by an equivalent amount of inspiratory effort before inspiratory flow can commence.

The physiologic and mechanical derangements associated with respiratory failure can be reverse by application of NIV through physiological effects such as:

- Increase intrathoracic pressure.
- Prevents airway and alveolar collapse,
- Improves oxygenation
- Reduces left ventricular after load with increase in cardiac output
- Decreased work of breathing
- Augments alveolar ventilation
- Decrease in respiratory rate (RR)
- Reduces transdiaphragmatic pressure, pressure time index
- Increases tidal volume
- Resetting of respiratory center ventilatory responses to $PaCO_2$,

Non-invasive ventilation shown to reduce the rate of intubation, mortality and ICU length of stay in hypercarbia respiratory failure due to acute exacerbation of COPD and in hypoxic respiratory failure in immunocompromised.

INDICATIONS OF NIV

Acute Exacerbation of COPD

Non-invasive ventilation has become the gold standard for mild or severe forms of acute exacerbation of COPD, as a means of improving alveolar ventilation, reducing the patient's work of breathing and avoiding the need for endotracheal intubation and its related complications. Severe forms of exacerbations associated with hypercapnic coma can also be treated with NIV under careful monitoring. COPD acute exacerbation is the largest single diagnostic category among NIV recipients. It not only improves vital sings but also dyspnea scores improves significantly. Success rate in avoiding intubation is 58–93% in various studies thus decreases morbidity and mortality rates.

Acute Cardiogenic Pulmonary Edema

The recommended first-line option for respiratory support is CPAP (10 cm H_2O appeared to be safe and effective) in moderate or severe cardiogenic pulmonary edema. Bi-level NIV and CPAP have equivalent impact on respiratory parameters but may have different effects on myocardial function. CPAP reduces preload and afterload and myocardial catecholamine release, but the cyclic pressures of bilevel positive airway pressure (BPAP) may case preload and afterload to rise and fall during respiration.

Community-acquired pneumonia with ARF

Despite numerous clinical reports of successful use of NIV in setting of community-acquired pneumonia (without COPD) and other forms of acute lung injury (ALI) in reducing respiratory distress as well intubation rate, the failure rate remains high.

Mechanical ventilation when used in immunocompromised patients with pneumonia it is associated with high morbidity and mortality. Use of NIV in these patients reduces the rate of intubation but whether it really improves survival is not clear.

INDICATIONS OF NIV IN OTHER ACUTE CONDITIONS

In acute exacerbation of bronchial asthma work of breathing increases because of increased resistance and intrinsic PEEP which increases the resistive and threshold respiratory work. It has been demonstrated that application of CPAP and Bi-level NIV in acute asthmatics achieves

by mansdocs.com

physiological and clinical improvement. Nebulised drugs can be effectively delivered in presence of high flow NIV circuit. But still strong clinical evidences required by controlled clinical studies as compared to the use in COPD acute exacerbation.

- Acute severe bronchial asthma
- Acute exacerbation in bronchiectasis/ interstitial lung disease (ILD)
- Chest trauma
- Immunosuppressed patients with ARF
- Patients of ARF who refuse intubation
- *Patients with ARF unsuitable for invasive ventilation*: Terminal cancer patients/end stage ILD
- ARF in neuromuscular disorders
- Weaning (failing T-tube trial but otherwise fit for extubation)
- Postextubation respiratory failure
- Postoperative respiratory failure.

INDICATIONS OF NIV IN CHRONIC CONDITIONS

- *Thoracic cage abnormalities*:
  - Chest wall deformities
  - Kyphoscoliosis
  - Spinal cord injury
  - Sequelae of polio.
- Progressive (rapidly and slowly) neuromuscular conditions [e.g. amyotrophic lateral sclerosis (ALS)]
- Myopathic/neuropathic disorders
- Sleep apnea syndromes and chronic hypoventilation syndromes.

SELECTION GUIDELINES IN COPD PATIENTS

Step 1: Identify patients in need of ventilatory assistance

- *Symptoms and signs of acute respiratory distress*:
  - Moderate to severe dyspnea, increased over usual
  - RR more than 24, accessory muscle use, paradoxical breathing
  - *Gas exchange abnormalities*:
    - $PaCO_2$ more than 45 mm Hg, pH less than 7.35 or
    - $PaO_2/FiO_2 < 200$
- *Symptoms and signs of chronic respiratory failure:*
  - Fatigue, hypersomnolence, dyspnea
  - ABG shows pH less than 7.35, $PaCO_2$ more than 55 mm Hg,
  - Oxygen saturation less than 88% for more than 10 minutes of monitoring time despite O_2 supplemental

Step 2: Exclude those with increased risk

- Respiratory arrest
- Medically unstable (hypotensive shock, uncontrolled cardiac ischemia or arrhythmias)
- Unable to protect airway (impaired cough or swallowing)
- Excessive secretions
- Agitated or uncooperative
- Facial trauma, burns or surgery, or anatomic abnormalities interfering with mask fit.

VENTILATORS USED TO PROVIDE NIV

Even if any ventilator can be used to start NIV in acute respiratory failure, success is more likely if the ventilator is able to adequately compensate for leaks; let the clinician continuously monitor patient-ventilator synchrony and ventilator parameters due to display of pressures-flow-volume waveforms and a double limb circuit; adjust the fraction of inspired oxygen with a blender to assure stable oxygenation; and adjust inspiratory trigger sensitivity and expiration cycling as an aid to manage patient-ventilator asynchronies.

Non-invasive ventilation is usually delivered either by Bi-level or by ICU ventilators. Even if able to efficiently compensate for air leaks, traditional Bi-level ventilators have some technical limitations (CO_2 rebreathing due to their single-limb circuit in non-vented masks; inadequate monitoring; lack of alarms and O_2 blending) which have been largely overcome by the newer generations of machines. Conversely, conventional ICU ventilators are not able to cope with leaks but allow good monitoring of ventilatory parameters as well as find setting of FiO_2 and of ventilation.

The choice of ventilator should not only be tailored to the pathophysiology and the severity of ARF but costs and staff experience should also be taken into account.

Minimum Performance Characteristics for Ventilators Providing NIV

- Mandatory rate ~ to 30 breaths/min
- Patient trigger capabilities yes
- FiO_2 0.21–0.5
- Inspiratory pressure to 30 cm H_2O
- PEEP to 15 cm H_2O
- 2-hours battery back-up optional

by mansdocs.com

- Pressure relief yes
- Antiasphyxia capabilities yes
- Airway attachments mask/mouthpiece
- Rebreathing potential minimal
- Inspiratory flow 60 L/min at 20 cm H_2O
- Circuit yes
- Humidification optional

Equipment Required to Initiate NIV

- Non-invasive ventilator
- Range of full face and nasal masks with sizing devices
- Ventilator tubing
- Exhalation valve/port (may be integral with ventilator tubing)
- Microbiological filter
- Head gear
- Skin necrosis patches
- Large sterile wipes to disinfect masks between use in patients.

Suggested NIV Settings

Inspiratory pressure	Initial	8–10 cm H_2O
	Eventual	12–20 cm H_2O
Expiratory pressure	Initial	4–5 cm H_2O
	Eventual	4–8 cm H_2O
Higher pressure for	Auto-PEEP, Improving oxygenation, Eliminating obstructive apnea	

Oxygenation and Humidification During NIV

- Bi-level ventilator:
  - Oxygen is administered up to 15 L/min
    - Into ports in the mask
    - Via a T-piece at the proximal end of the venti lator tubing
    - *Maximal level of FiO_2*: 45–50%
- Critical care ventilator:
  - Desirable FiO_2 selected from oxygen blender
- Heated pass-over humidifier is preferred
- Heat-and-moisture exchangers should be avoided.

Monitoring

- *Physiological*:
  - Continuous oximetry
  - Exhaled tidal volume
  - Obtain ABG-s within an hour and q 2–6 hours or as needed.
- *Objective*:
  - Respiratory rate
  - Blood pressure
  - Pulse rate.
- *Subjective*:
  - Dyspnea
  - Mental alertness
  - Comfort.
- *Mask*:
  - Fit, comfort, air leak, skin necrosis and secretions.
- *Respiratory muscle unloading*:
  - Accessory muscle activity
  - Paradoxical abdominal motion.
- *Abdomen*:
  - Gastric Distention.

Triggering

- Ventilator triggering is critical to the success of NIV
- Trigger sensitivity and ventilator response times are generally good with NIV machines (Figs. 1A and B).
- Ineffective triggering (Fig. 2) imposes significant load on work of breathing and causes discomfort to the patient.

Termination of Inspiration

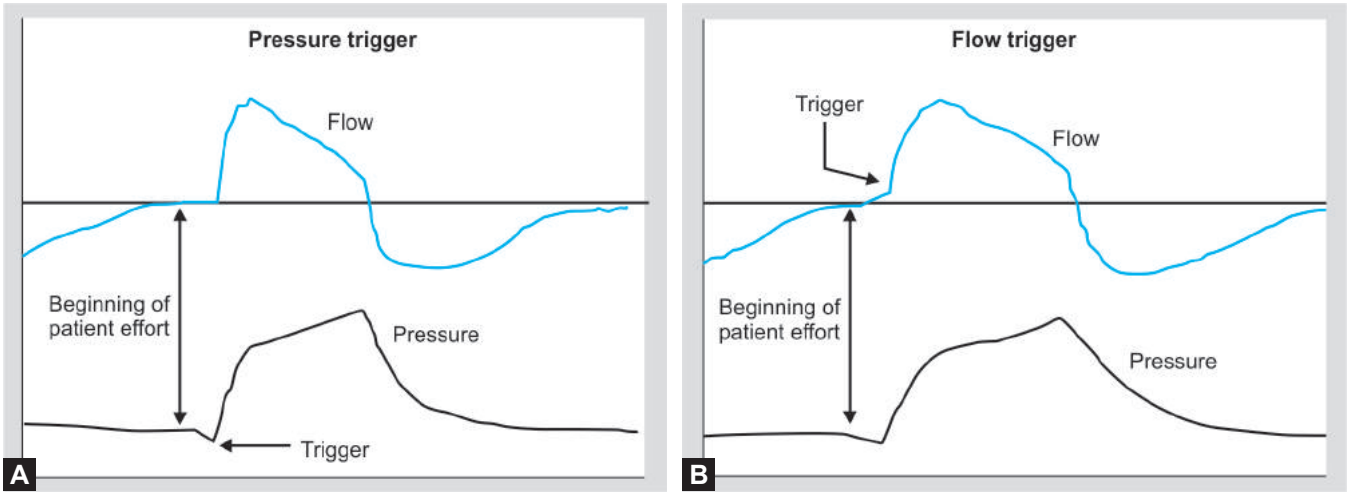
- *Primary method*: Patients inspiratory flow decreases to a predetermined level
- *Secondary termination criteria*: End inspiratory pressure exceeds target level
- *Tertiary termination criteria:* Lengthy inspiratory time (2–3 seconds).

The First Hour of Initiating NIV

- Titrate settings and FiO_2
- Adjust to reduce work of breathing and respiratory rate
- Assist patient comfort and tolerate mask
- Use minimal sedation
- Monitor Mental status
- *If worsening*: Intubate
- Keep patient NPO initially
- Check ABG-s in 1–2 hours.

In general, NPPV should be instituted in a setting that offers close monitoring and the ability for intervention. Improvement in patient comfort, $PaCO_2$ and respiratory acidosis over 1 or 2 hours indicates successful NPPV.

by mansdocs.com



Figs. 1A and B: (A) Pressure trigger; (B) Flow trigger.

DETERMINANTS OF NIV SUCCESS IN COPD PATIENTS

- Younger age
- Lower acuity of illness (APACHE/SAPS score)
- Able to cooperate; better neurologic score
- Able to coordinate breathing with ventilator
- Less air leaking, intact dentition
- Hypercarbia, but not too severe ($PaCO_2$ > 45 mm Hg, but < 92 mm Hg)
- Acidemia, but not too severe (pH< 7.35, > 7.10)
- Improvements in gas exchange and heart rate and respiratory rate (RR) within first 2 hours.

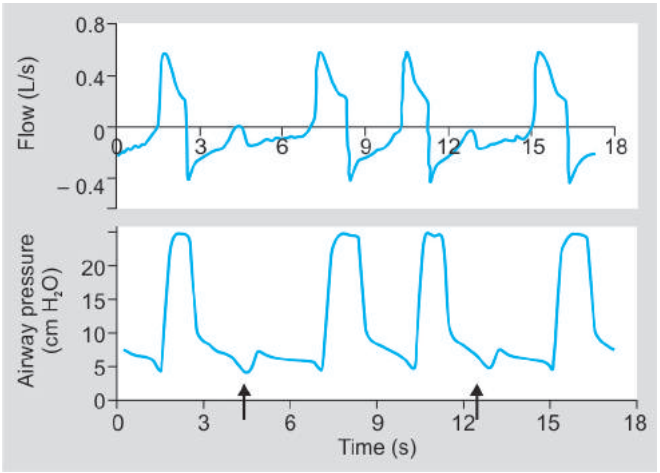


Fig. 2: Ineffective triggering.

NON-INVASIVE VENTILATION FAILURE

- Worsening encephalopathy or agitation
- Inability to clear secretion
- Inability to accept any interface
- Hemodynamic instability
- Worsening oxygenation
- Progressive hypercapnia, pH less than 7.20
- Persistent tachypnea/tachycardia.

Contraindications and complications specific to NIV are listed as follows:

- *Contraindications*:
  - Respiratory arrest
  - Unprotected airway (coma, sedation)
  - Upper-airway obstruction
  - Inability to clear secretions
  - Untreated pneumothorax
  - Marked hemodynamic instability
- *Complications*:
  - Mask discomfort, patient intolerance
  - Facial or ocular abrasions
  - Nasal congestion, sinus pain
  - Oronasal dryness
  - Intraocular pressure (particularly in patients with glaucoma)
  - Intracranial pressure (particularly in patients with neurotrauma)

by mansdocs.com

- Blood pressure (if hypovolemic)
- Aspiration pneumonia (rare)
- Aerophagia and gastric distension (uncommon; routine gastric decompression is unnecessary).

EMERGING MODES OF NON-INVASIVE VENTILATION

In PSV specially delivered through NIV the preset pressure does not vary in the presence of modifications of the respiratory system impedance, secondary to change in airway resistance and pulmonary and/or chest wall compliance, so that alveolar hypoventilation may occur. To overcome this draw back, average volume-assured pressure support has been proposed. A further challenging approach to improve patient-ventilator interaction would be to match ventilator support with neural output of the respiratory centers. Two modes, proportional assist ventilation (PAV) and neutrally adjusted ventilatory assistance (NAVA) have been developed for this purpose. Few studies have evaluated to use NAVA and PAV to deliver NIV.

BIBLIOGRAPHY

1. Abramson MJ, Crockett AJ, Frith PA, et al. COPDX: an update of guidelines for the management of chronic obstructive pulmonary disease with a review of recent evidence. Med J Aust. 2006;184(7):342–5.
2. Duke G, Bersten AD. Non-invasive ventilation. In: Bersten AD, Soni N (Eds). Oh's Intensive Care Manual, 6th edition. Butterworth Heinemann Elsevier; 2009. pp. 429-37.
3. Meduri GU, Turner RE, Abou-Shala N, et al. Noninvasive positive pressure ventilation via face mask. First line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest. 1996;109(1):179-93.
4. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001;163(2):540-77.
5. Nava S, Carbone G, DiBattista N, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. Am J Respir Crit Care Med. 2003;168(12):1432-7.
6. Ram FS, Picot J, Lightowler J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(3):CD004104.
7. Storre JH, Seuthe B, Fiechter R, et al. Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. Chest. 2006;130(3):815-21.

by mansdocs.com

CHAPTER

77

Ventilation Strategy in Obstructive Airway Disease

Rajesh Pande, Atul Pathak

INTRODUCTION

Severe asthma exacerbation causing respiratory failure remains a potentially reversible, life-threatening condition that imposes significant morbidity and mortality. About 10% of asthmatics admitted to hospital go to intensive care unit (ICU), with 2% being intubated. Admission to ICU and need for mechanical ventilation are associated with morbidity and mortality. ICU admission identifies an asthmatic patient as a member of a poor prognostic group. Death is most commonly a result of one of the complications of airflow obstruction and severe gas trapping. These complications include barotrauma, hypotension and refractory respiratory acidosis.

PATHOPHYSIOLOGY

- *Airflow obstruction*: As a result of critical increase in airway resistance, high pressures required for airflow may overload respiratory muscles (ventilatory pump failure). Regions of lung cannot properly empty and return to their "resting volume" (air trapping) → intrinsic positive end expiratory pressure (iPEEP)/auto-PEEP (auto-positive end expiratory pressure) → further worsens respiratory muscle function.
- Overinflated regions may compress healthy regions → V/Q mismatch. Air trapping and iPEEP also function as a threshold load to trigger mechanical breaths.
- *Worsening airflow obstruction*: Decreased minute ventilation due to respiratory muscle overload. Hypercapnic respiratory failure. V/Q mismatch due to regional lung compression and regional hyperventilation. Increased dead space and loss of capillaries due to overdistension and emphysematous changes. Overload on right ventricle due to hypoxic pulmonary vasoconstriction and chronic vascular changes.
- Severe asthma exacerbation → bronchoconstriction, airway edema and/or mucous plugging → severe airflow limitation. Work of breathing (WOB) is significantly increased. Expiration becomes active in an attempt by the patient to force the inspired gas out of their lungs. Increased inspiratory work due to high airway resistance and hyperinflation. Lungs and chest wall operate on a suboptimal portion of their pressure–volume curves.
- Gas trapping occurs because low expiratory flow rates mandate long expiratory times if the entire inspired volume is to be exhaled. If the next breath interrupts exhalation, then gas trapping results. Trapped gas in lungs results in additional pressure at end expiration (auto-PEEP or intrinsic PEEP) above applied PEEP, leading to dynamic hyperinflation. Auto-PEEP, intrinsic PEEP and dynamic hyperinflation are terms that are frequently used interchangeably.

Dynamic hyperinflation: Failure of lung to return to its relaxed volume or functional residual capacity (FRC) at end-exhalation. Hyperinflation can be adaptive. With higher lung volumes, the increase in airway diameter and elastic recoil pressure enhances expiratory flow. But excessive dynamic hyperinflation can cause hypotension and barotrauma during mechanical ventilation of severe asthma. These developments are the usual causes of excess morbidity and mortality. It can be measured in

by mansdocs.com

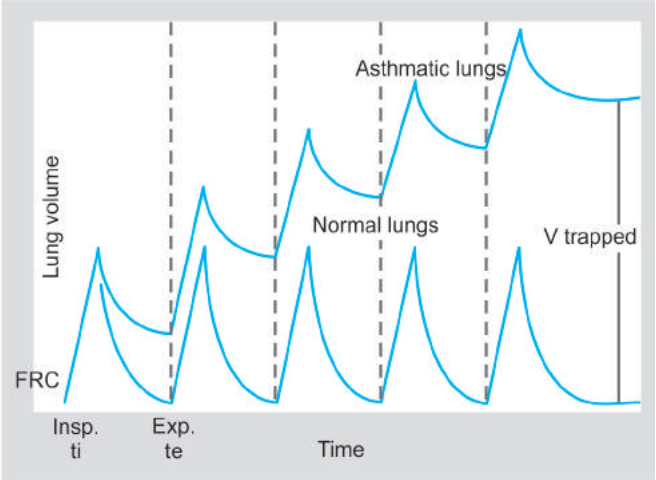


Fig. 1: Dynamic hyperinflation in setting of severe airflow obstruction (FRC: Functional residual capacity).

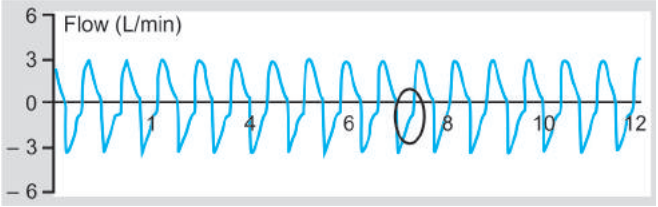


Fig. 2: Flow waveform demonstrates gas trapping. The decelerating expiratory limb fails to reach the baseline before the next breath begins (circled), preventing complete emptying of the lung

various ways involving volume, pressure, or flow of gas. Total exhaled volume during 20–60 s of apnea in a paralyzed patient can give estimate of trapped gas. ('VEI'—volume of gas trapped, volume of gas at end-inspiration above FRC). VEI more than 20 mL/kg predicts hypotension and barotrauma in ventilated patients with severe asthma (Fig. 1).

Occult positive end expiratory pressure: All airways may not be in communication with the proximal airway in severe asthma (complete airway closure in those segments). Occult auto-PEEP has all bad effect of auto-PEEP but it cannot be quantified easily. Good clinical judgment is important. Clinicians should question low auto-PEEP measurements in situations that suggest otherwise.

Examples of occult auto-positive end expiratory pressure: When the increase in end inspiratory plateau pressure (Pplat) is not explained by the decrease in respiratory system compliance during volume-cycled ventilation, Pplat measurement should be done and for reliable measurements, the patients must be paralyzed or heavily sedated. Pplat reflects gas trapping because as lung volume increases, the alveolar pressure also increases (assuming there is no other explanation such as adjustments to the ventilator or changes in respiratory system compliance).

Decreased volumes during pressure controlled ventilation (PCV) may indicate gas trapping. The chest wall girth may increase and increased hyperinflation on chest imaging. The ventilation becomes inefficient increasing the patient effort. Clinically it may manifest as unexplained patient agitation, barotrauma, hemodynamic compromise, missed respiratory efforts (as patients attempt to trigger the ventilator but cannot generate enough pressure to overcome the auto-PEEP that has developed). Gas trapping can be measured by observing the flow versus time graphics on the ventilator and if the inspiratory flow begins before expiratory flow ends, it suggests that gas is trapped in the lungs. (Fig. 2).

VENTILATION IN ASTHMA

When severe asthma does not respond to medical therapy, we must intervene fast to provide adequate oxygenation and ventilation. The choices are noninvasive ventilation (NIV) or invasive ventilation.

Noninvasive ventilation: It is possible that some patients with severe asthma may benefit from NIV. In selected patients NIV could improve lung function and possibly reduce the need for hospitalization. In chronic obstructive pulmonary disease (COPD) with severe airflow limitation—a number of prospective randomized trials have shown that NIV reduces the need for endotracheal intubation, length of hospital stay and in-hospital mortality rate, and even that it improves long-term survival.

The role of NIV in acute asthma is at best controversial. While no guidelines have been established, a reasonable approach would be to use NIV in patients who do not respond to initial medical therapy, and have no contraindications for the use of NIV.

Invasive ventilation: The objective of initiating invasive ventilation is to limit gas trapping by controlled hypoventilation. It can be achieved by reducing tidal volume, and frequency resulting in less gas to exhale over longer expiratory time, thereby reducing gas trapping. The expiratory flow resistance should be relieved by airway suctioning, bronchodilators, steroids, and using a large-bore endotracheal (ET) tube. The inspiratory time is reduced by increasing the inspiratory flow (70–100 L/min) or incorporating non-distensible tubing. The need for high minute

by mansdocs.com

ventilation should be reduced by reducing CO2 production, by using sedation/paralysis and controlling fever or pain. The application of external PEEP in severe asthma is controversial. The theoretical advantages of PEEP application include decreased WOB and hence CO2 production, while limiting gas trapping by splinting the airways open. A decreased inspiratory muscle effort is required to overcome auto-PEEP and initiate an inspiration. But in practice, application of external PEEP may increase total PEEP and worsen gas trapping.

It is, however, useful in COPD with airflow obstruction, where more than 40% of inspiratory muscle effort can be expanded to overcome auto-PEEP. By adding extrinsic PEEP, the inspiratory muscle effort needed to trigger inspiration can be attenuated. In such patients extrinsic PEEP must be titrated individually with an average of 80% of the auto-PEEP being tolerated before the plateau pressures and total PEEP begins to increase. It is useful in patients who are breathing spontaneously and capable of triggering the ventilator. However, if extrinsic PEEP is more than auto-PEEP, gas trapping will worsen. It is sometimes difficult to measure auto-PEEP reliably as the significant auto PEEP imposed by the non-communicating alveoli cannot be measured (occult PEEP). The recommendations for using external PEEP are either to use it minimally or not at all in patients with severe asthma. The pros & cons of using extrinsic PEEP must be weighed (reductions in auto-PEEP vs worsening gas trapping) besides careful bedside observation and frequent monitoring of total PEEP in heavily sedated or paralyzed patients.

by mansdocs.com

CHAPTER

78

Ventilation Strategy in Trauma

Vikas Maurya

INTRODUCTION

In the realm of trauma and critical care, most commonly intensivists are challenged in the management of patients demonstrating chest and brain injury. The highlight of the chapter is how to manage patient on ventilator when they got traumatic brain injury (TBI) or chest injury.

TRAUMATIC BRAIN INJURY

Traumatic brain injury has been termed as a silent global epidemic. It accounts for up to 30% of all trauma-related deaths and is the leading cause of death in the developed countries. Before talking about ventilator management it is important to know about the following important indices.

Intracranial Pressure

- This is the pressure of the brain, cerebrospinal fluid and the brain's blood supply within the intracranial space.
- Since the skull is basically a closed system, an increase in volume will produce an increase in pressure.
- Elevated intracranial pressure (ICP) can also affect the perfusion of the brain.
- Elevated ICP is one of the most damaging aspects of neurological trauma, and is directly related to poor prognosis.

Cerebral Perfusion Pressure and Cerebral Blood Flow

- Cerebral perfusion pressure (CPP) is measured by taking the mean arterial pressure and subtracting ICP.
- Cerebral blood flow (CBF)—determined in part by CPP
- CBF—maintained at a constant rate in the presence of changing CPP by local myogenic and metabolic autoregulation.

Relation between CBF and ICP following TBI is shown in Figure 1.

Normal physiological relationship between CBF and $PaCO_2$ and PaO_2 is shown in Figure 2.

Intubation in TBI

During laryngeal intubation, the normal body's reaction is to get agitated. This causes hypertension as well as rise

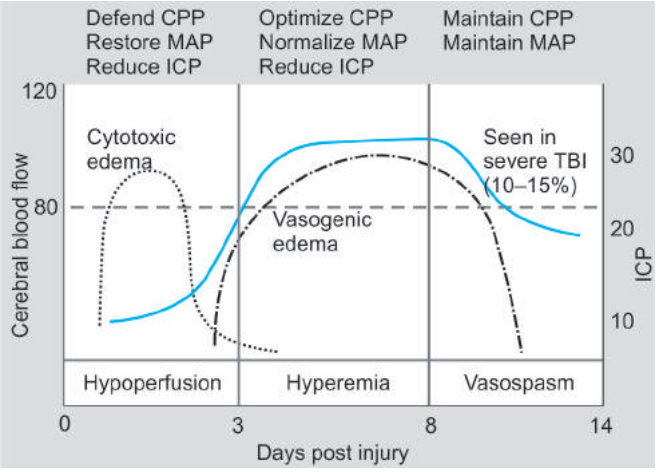


Fig. 1: Relationship between cerebral blood flow and intracranial pressure (ICP) over time following traumatic brain injury (TBI).
(CPP: Cerebral perfusion pressure; MAP: Mean arterial pressure).

by mansdocs.com

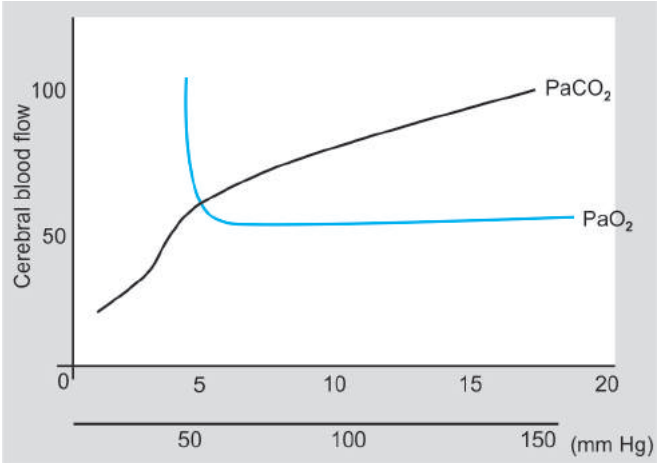


Fig. 2: The relationship between CBF and $PaCO_2$ and PaO_2.

in ICP. Therefore adequate premedication for intubation is essential (Table 1).

Table 1: Premedication drugs.

Sedatives used	*Paralytics used*
• Sodium thiopental	• Rocuronium
• Propofol	• Succinylcholine
• Etomidate	

Intubation in TBI

Preferred method is preoxygenation and rapid sequence intubation (RSI). Along with RSI, cricoid pressure is to be given to prevent aspiration and in-line immobilization of cervical spine to be done in all patients. Cervical spine injury is to be assumed in all TBI patients unless proven otherwise. Though lidocaine use is not supported in "randomized clinical trials", it is used as is found to suppress the autonomic response from laryngeal stimulation.

Rapid sequence intubation—it involves administration of a sedative and a paralytic agent before intubation (minimize risk of gastric aspiration).

It is important to remember "6 P's" during intubation. These are:

Preparation, preoxygenation, premedication, paralysis, placement of tube and postintubation care.

Following intubation, it is important to start sedation in these patients as if left unsedated, there can be increase in ICP if patient gets agitated. The sedation of choice so far is propofol as it not only sedates the patient well, but also reduces the ICP. Secondly, once the patient is off propofol, its effect weans off rapidly. Other agents which can be used is midazolam, especially when the patient is hemodynamically unstable. It is also wise to start opioids like fentanyl to control pain in the patient with TBI. This is important as pain itself can cause rise in ICP.

Ventilation in TBI

Below is the strategy to be adopted in these patients:

- Adequate oxygenation and avoid hypercapnia.
- Target $PaCO_2$ = 36–40 mm Hg.
- Hyperventilation further reduces CBF in the early phase so patients in early phase should not be hyperventilated unless there are signs of raised ICP or impending herniation.
- Hyperventilation with $PaCO_2 \leq 30$ mm Hg can be done prior to urgent imaging or surgical evacuation of a mass lesion.
- If this strategy is used, be sure to go back to normocarbia gradually, as rapid normocarbia can cause rapid increase in blood flow leading to raised ICP.
- Positive end-expiratory pressure (PEEP) can also increase ICP by hampering the venous return to the heart by increasing intrathoracic pressure. The recommended PEEP is 5–10 cm H_2O to maintain functional residual capacity and oxygenation. The higher levels as told may compromise cerebral venous return and increase ICP. It is also important to have head of bed up especially when using PEEP.

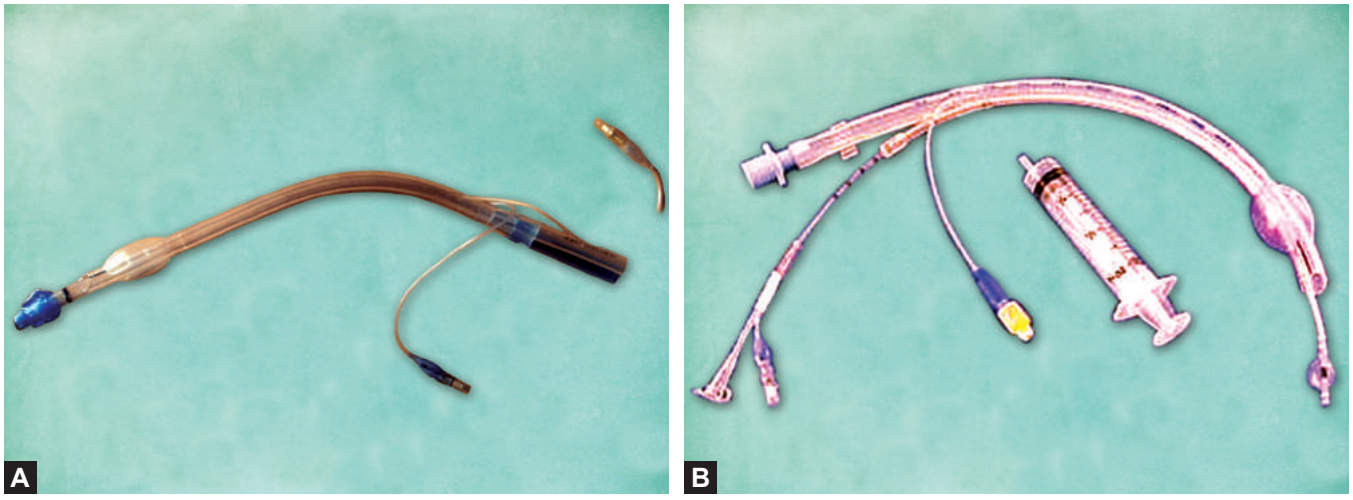
CHEST TRAUMA

A fundamental goal of critical care management is to avoid hypoxia and hypoventilation, the two main causes of mortality in the acute period following trauma. For most chest trauma patients, endotracheal intubation and chest tube insertion are the mainstays of treatment; however, a subset of these life-threatening injuries will require a more specialized approach.

Chest trauma can be divided into blunt or penetrating chest trauma. The pathophysiological mechanism leading to chest problem is two-way hit process, i.e. direct parenchymal damage by the injury and alveolocapillary changes caused by systemic inflammation.

Besides supportive management, conventional ventilation is an important aspect in the treatment of chest trauma.

by mansdocs.com



Figs. 3A and B: (A) Double lumen tube (DLT); (B) Univent tube with bronchial blocker.

Independent Lung Ventilation

Independent lung ventilation (ILV) is a method of mechanical ventilation in which the right lung and left lung are managed independently, either by anatomical or physiological separation. ILV was first use in 1931 in thoracic surgery. Its indication in critical care is poorly defined. ILV can either be one-lung ILV (OL-ILV) or two-lung ILV (TL-ILV). Of note, the usage of ILV is only possible because of the development of the double-lumen endotracheal tube (DL-ETT).

Recommendations of use of ILV

- *Level 1*—None
- *Level 2*—None
- *Level 3*—
  a. Independent lung ventilation should be considered in the patient with radiographically apparent unilateral lung disease and one or more of the following:
     i. Hypoxemia refractory to high FiO_2 and PEEP.
     ii. PEEP-induced deterioration in oxygenation or shunt fraction.
     iii. Overinflation of the noninvolved lung with or without collapse of the involved lung.
     iv. Significant deterioration in circulatory status in response to PEEP.
  b. Independent lung ventilation should be considered in the patient with bronchopleural fistula (BPF) who demonstrates one or more of the following:
     i. Air leak exceeding 50% of the delivered tidal volume (TV).
     ii. Hypercapnic respiratory acidosis (pH < 7.30).
     iii. Refractory hypoxemia particularly in patients in whom increases in PEEP exacerbate air leak.
     iv. Persistent lung collapse despite optimum catheter drainage.
  c. Invasive hemodynamic monitoring is frequently advisable to monitor the effect of ILV on cardiac output and intrapulmonary shunt.

In OL-ILV, main or subsegmental bronchus is blocked mechanically whereas in TL-ILV, independent ventilator circuits are used for each lung, working either synchronously or asynchronously.

There are several techniques available to achieve this goal, ranging from a simple mainstem bronchus intubation to the use of DL-ETT or placement of bronchial blocker with SL-ETT or a univent tube (Figs. 3A and B). All of these techniques can be performed blind but are preferably guided by a bronchoscope.

It is important to understand about the size of the double lumen tube (Table 2), its correct placement and confirmation:

- For most adults, 39–41 F size tube is used. Stylet should be used.
- Tube is passed with endobronchial curvature forward.
- Stylet is removed and tube is rotated 90° toward the side of placement.
- Depth of tube: The 29 cm mark should be at the mouth for patients (male or female) with a height of 170 cm.
- One centimeter change with each 10 cm change in height.

by mansdocs.com

Table 2: Double-lumen endotracheal tube—size and application.

Tube size (F)	Circumference (mm)	Lumen diameter (mm)	Indications
28			Pediatrics < 40 kg (> age 4–5)
35	38	5	> 40 kg children
37	40	5.5	Small adults
39	44	6	Medium-sized adults; usual female size
41	45	6.5	Large adults; usual male size

- Confirmation of the placement of the tube to be done with auscultation, but fiberoptic bronchoscopy is better.
- Confirming functional separation can be done with water bubble technique or balloon technique.
- It is important to use sedation and if required neuromuscular blocking agents to prevent tube displacement.
- Displacement can be monitored by using end-tidal CO_2 ($EtCO_2$), peak inspiratory pressure (PIP) and continuous spirometry.

Independent Lung Ventilation

- *Synchronous TL-ILV*:
  - Respiratory rate, cycle in phase or out of phase should be same both machines
  - Inspiratory flow rate, TV and PEEP may be set indenpendently
  - Two ventilators with special software are synchronized by an external cable.
- *Asynchronous TL-ILV*:
  - Must use two separate ventilators
  - Different ventilator settings/modes.
- *Anatomical separation*:
  - Useful in chest trauma with unilateral endobronchial bleed
  - OL-ILV = SL-ETT with bronchial blocker/DL-ETT.
- *Physiological separation:*
  - Each lung ventilated as a separate unit
  - DL-ETT and TL-ILV
  - Can be used in asymmetric pulmonary contusion, massive air leaks (MAL) or BPF, bronchial injury.
- *Initial ventilatory settings*:
  - 5 mL/kg in the normal lung: 2 mL/kg in the diseased lung
  - Plateau pressure (Pplat) less than 30 cm H_2O or even less than 26 cm to the diseases lung.
- *Monitoring during ILV*:
  - Each circuit's Paw, Pplat, Compliance
  - $EtCO_2$.
- *Criteria for switching from TL-ILV to SL-ETT conventional mechanical ventilation (CMV)*:
  - Equalization of TV use (or difference < 100 mL)
  - $EtCO_2$ level on both disease lung and normal lung
  - Compliance (differ by at least 20%) of both lung.

Clinical Scenarios and their Management

- *Pulmonary Contusion (with respiratory compromise)*:
  - Prophylactic intubation should be done
  - If CMV fails, TL-ILV low TV strategy in diseased lung should be used
  - Combined synchronized PC-IRV and high frequency oscillatory ventilation (HFOV) with TL-ILV has also been used.
- *Bronchopleural fistulas and MAL*:
  - Massive air leaks usually from many disparate sources or blunt injury
  - Bronchopleural fistulas typically through single discrete pathway— penetrating injury, surgery, infection
  - HFOV, ILV.
- *Tracheobronchial injury*:
  - No direct signs and CT scan may fail
  - Indirect signs—pneumothorax, subcutaneous emphysema, pneumomediastinum, or non-expanding lung after chest tube insertion.
  - Fastest and most reliable test to detect tracheobronchial injury is fiberoptic bronchoscopy.
  - After emergent surgical repair, TL-ILV to protect the anastomosis.
- *Acute bilateral lung injury*:
  - Controversial indication for ILV
  - HFOV with SL-ETT.

SUMMARY

Traumatic brain injury and massive chest trauma are the most common injury for which the patient is admitted in the ICU. In TBI, it is important to prevent rise in ICP, to provide adequate oxygenation and to avoid hypercapnia. High PEEP should be avoided as far as possible. In patients with chest trauma, besides conventional ventilation, it is important to be aware of ILV and it should be a part of intensivist's armamentarium.

by mansdocs.com

BIBLIOGRAPHY

1. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24 (Suppl 1):S1-106.
2. Burton NA, Watson DC, Brodsky JB, et al. Advantages of a new polyvinyl chloride double lumen tube in thoracic surgery. Ann Thorac Surg. 1983;36(1):78-84.
3. Hayes M. Cerebral protection. In: Bersten AD, Soni N Oh TE (Eds). Oh's Intensive Care Manual, 5th edition. Philadelphia, PA: Butterworth-Heinemann Press; 2003. pp. 505-14.
4. Rico FR, Cheng JD, Gestring ML, et al. Mechanical ventilation strategies in massive chest trauma. Crit Care Clin. 2007;23(2):299-315.

by mansdocs.com

CHAPTER

79

Rescue Strategies in ARDS—Recruitment Maneuvers

Rajesh Pande, Anupam Basumatari

Rescue strategies (Flowchart 1) should be employed in patients with refractory acute respiratory distress syndrome (ARDS)—after initial ARDS net ventilation strategy has been employed and the goals have not been achieved. The goals are:

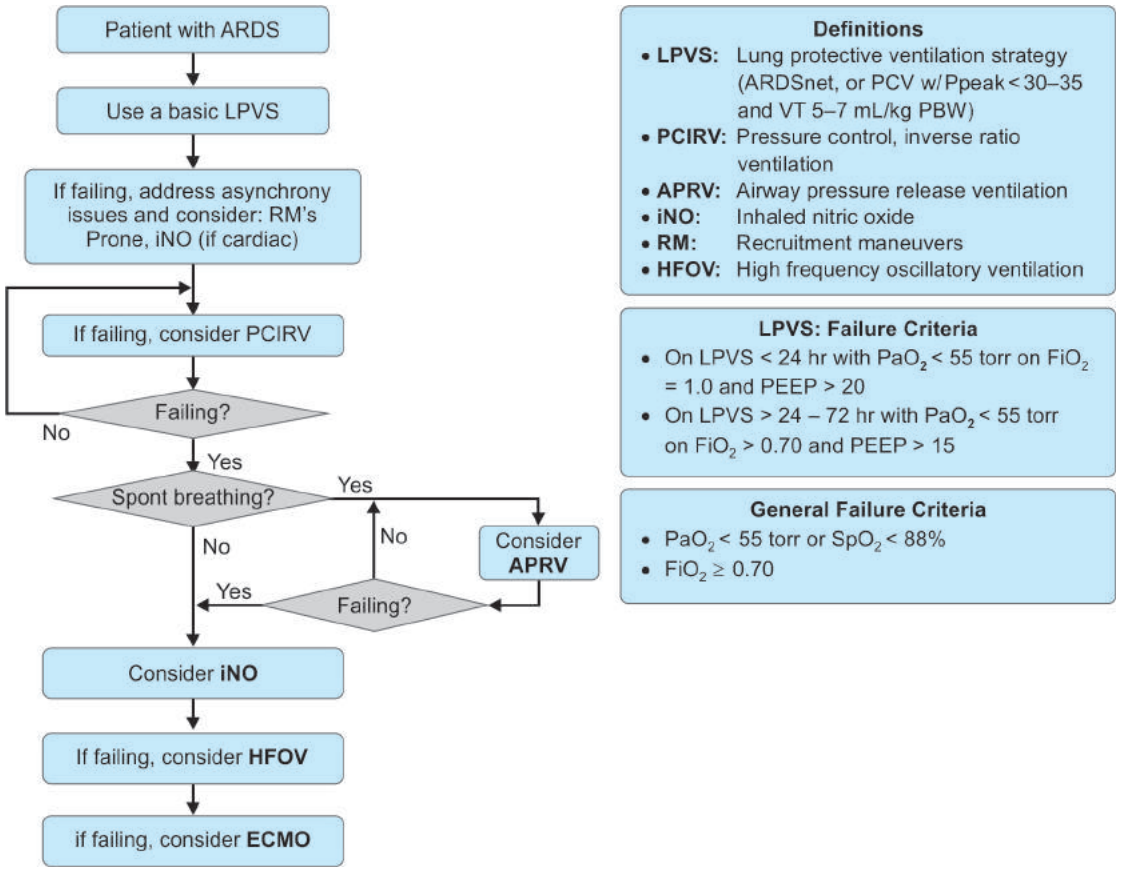
Oxygenation goal: PaO_2 55–80 mm Hg or SpO_2 88–95%

Plateau pressure goal: Less than or equal to 30 cm H_2O

pH goal: 7.3–7.45

Fractional inspired oxygen (FiO_2) less than 60%.

Flowchart 1: Rescue strategy algorithm in acute respiratory distress syndrome.



by mansdocs.com

RECRUITMENT

Recruitment is a dynamic process of reopening previously collapsed lung units through an intentional increase in transpulmonary pressure. Some potentially recruitable units require opening pressures that exceed safe limits for tidal ventilation and process of tissue recruitment continues until further expansion is constrained by total lung capacity. It basically means blow hard (to reinflate collapsed alveoli) and maintain the blow (to prevent derecruitment by applying positive end expiratory pressure (PEEP) after the maneuver), and is in fact an administration of high ventilation pressure for a brief period of time.

The benefits of recruitment:

- Increases the end-expiratory lung volume
- Improves gas exchange
- Reduces strain of ventilation and
- Prevents repetitive opening and closing of unstable units, thereby reducing ventilator-induced lung injury (VILI)
- Recruitment maneuver (RM) for severe hypoxia should be used early while ensuring hemodynamic stability. Multiple recruitment maneuvers may be required. Postrecruitment positive end-respiratory pressure (PEEP) should be applied. RM should also be applied after interventions, which can cause derecruitment like ventilator disconnection and endotracheal suctioning. But long-term gains in oxygenation or lung mechanics may not be achieved.

Types of Recruitment Maneuver

- *Traditional method*: Sustained inflation (SI) → 30/30, 40/40. The reasoning behind this is unclear
- *Sustained inflation maneuver*: Most commonly used
- Continuous pressure of 35–50 cm H_2O for up to 30–60 seconds.
- *Use PS/CPAP mode*: Set PS = 0, PEEP = 40 cm H_2O
- *Control mode*: Inspiratory hold for 30–60 seconds
- Volume control ventilation with PEEP = 20 cm H_2O, allowing Ppeak to go up to 40 cm H_2O for 2 minutes, and then gradually reducing PEEP
- Pressure controlled ventilation with Pplat 45 cm H_2O, PEEP = 5 cm H_2O, I:E 1:1 and rate of 10 for 2 minutes
- Intermittent sighs (three consecutive sighs at 45 cm H_2O pressure) in volume or pressure control mode.

Slow Recruitment Maneuver

- *Incremental PEEP limiting the maximal inspiratory pressure. PC mode*: Peak inspiratory pressure (PIP) 35 cm H_2O, PEEP increment by 5 cm H_2O every 30 seconds to 35 cm H_2O for 30 seconds
- *Extended sigh*: PEEP maintained at 10 cm H_2O above the lower inflection point of the pressure-volume curve for 15 minutes
- Intermittent increase in PEEP for two breaths every minute
- Increasing PIP by increments of 10 cm H_2O to levels greater than 60 cm H_2O for brief periods
- Long slow increase in inspiratory pressure up to 40 cm H_2O (RAMP)
- *Volume control mode*: PEEP elevation up to 15 cm H_2O and end-inspiratory pauses for 7 seconds twice per minute for 15 minutes
- *Prolonged recruitment maneuver*: Step-wise increase in PIP of 15 cm H_2O → 20 cm H_2O → 25 cm H_2O above a PEEP of 15 cm H_2O (maximal PIP = 40 cm H_2O) with interposed periods of PIP = 10 cm H_2O.

Which Patients Will Benefit More?

- Early ARDS (< 7 days)
- Diffuse (secondary) ARDS
- Severe disease
- Compliant chest wall (vs stiff chest wall)
- Prone position
- Use of postrecruitment PEEP.

How to Identify Recruitable Lung?

- Use computed tomography (CT) to identify potentially recruitable lung
- Proportion of total lung weight accounted for by nonaerated lung tissue in which aeration was restored (CT) by an airway pressure of 45 cm H_2O from an airway pressure of 5 cm H_2O.
- *Bedside estimate of potentially recruitable lung*:
  - Changes in P/F ratio (improved)
  - $PaCO_2$ (decreased)
  - Percentage of alveolar dead space (decreased)
- Respiratory system compliance (improved)
- Potentially recruitable lung by CT = 13 ± 11% of total lung weight. Percentage of potentially recruitable lung was independent predictor associated with incidence of death.

by mansdocs.com

In early onset ARDS, most recruitment occurs during first 10 seconds of a sustained RM. Hemodynamic impairment is significant after the 10th second.

Contraindications to Recruitment Maneuver

- Hemodynamic instability
- *Increased intracranial pressure*: Head injury
- *Existing barotrauma*: Air leaks/pneumothorax
- *Predisposition to barotrauma*:
  - Apical bullous lung disease, necrotizing pneumonia, lung cysts
  - Focal lung pathology, e.g. lobar pneumonia
- *Relative contraindication*: ARDS more than 1 week.

Discontinue the Maneuver If

- Systolic BP decreases by 30 mm Hg
- SaO_2 decreases by 5% (transient decrease is common)
- Heart rate increases by 20/minute
- Arrhythmia is seen.

Adverse Events and Mortality

- *Hypotension*: 12% (usually transient and self-limited)
- *Desaturation*: 8%
- *Barotrauma*: 1%
- *Arrhythmias*: 1%
- *Rescue maneuver terminated due to adverse event*: 1%
- *Mortality*: 38% (vs 34–58%)
- *Ventilator-induced lung injury*: Difficult to quantify
- Barotrauma; overdistension of already well-ventilated lung regions
- *Indirect adverse effects*: Increased sedation/paralysis requirement
- Increased intracranial pressure (ICP).

Other Concerns

Sustained high-pressure ventilation can cause translocation of bacteria from alveoli to capillaries and systemic distribution of cell or bacterial products that can trigger an inflammatory response with cardiac depression and possibly shock.

Risk of superinfection is always there in mechanically ventilated patients. Conversely, a focal bronchopneumonia can induce secondary septic shock and extrapulmonary lung injury. The primary/secondary story is very attractive and appears logical. The belief persists despite numerous studies unable to verify it. "There is no evidence to make conclusions on whether RMs reduce mortality or length of ventilation in patients with acute lung injury (ALI) or ARDS".[6]

BIBLIOGRAPHY

1. Crotti S, Mascheroni D, Caironi P, Pelosi P, et al. Recruitment and Derecruitment during Acute Respiratory Failure. Am J Respir Crit Care Med. 2001;164:131-40.
2. Gattinoni L, Caironi P, Cressoni M, et al. Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome. N Eng J Med 2006;354:1775-86.
3. Hodgson C, Keating JL, Holland AE et al. Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation. Cochrane Database Sys Rev. 2009; 15;(2):CD006667.
4. Pelosi P, Goldner M, Mckibben A, et al. Recruitment and Derecruitment During Acute Respiratory Failure. Am J Respir Crit Care Med. 2001; 164:164,122-30.
5. Serdar C, Ozge K, Ferdi M, et al. The Pulmonary and Hemodynamic Effects of Two Different Recruitment Maneuvers After Cardiac Surgery. Anesth Anal 2007;104:384-90.

by mansdocs.com

CHAPTER 80

Rescue Therapy in ARDS: Prone Ventilation and High Frequency Oscillation Ventilation (HFOV)

Rajesh Pande, Abhishek Vishnu

PRONE VENTILATION

It means ventilating the patient in a prone position (Figs. 1A and B). In a study published in 1974, AC Bryan described its use for the first time. The author showed increase in partial pressure of oxygen in arterial blood (PaO_2) in patients with acute respiratory failure when they were put in prone position. Since then numerous animal and human studies and case reports have been published regarding positive effects on PaO_2 in prone position when unable to maintain oxygenation in supine position.

Improvement in oxygenation has been attributed to better ventilation/perfusion (V/Q) matching. There is redistribution of ventilation, i.e. opening up of the alveoli in the dorsal areas of the lung as well. The heart and abdominal content has less compressive effect on the dependent regions of lung in prone position, resulting in opening of the collapsed alveoli. Perfusion is more evenly distributed resulting in a better V/Q matching.

Studied have even shown that recruitment maneuvers have better response during prone position. Due to opening of the collapsed alveoli and redistribution of ventilation, it has also been shown this leads to decrease and delay in occurrence of ventilator-induced lung injury (VILI) in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Various randomized controlled trials (RCTs) and systematic review have shown improvement in PaO_2/fraction of inspired



Figs. 1A and B: (A) Ventilation in prone position; (B) Patient being nursed in prone position.

by mansdocs.com

oxygen (FiO_2) ratio once patients with ARDS are put on prone ventilation. Recent meta-analysis has even shown that prone ventilation results in significantly improved mortality in patients with severe ARDS ($PaO_2/FiO_2 < 100$).

Longer duration of prone position has been found to be better in improving oxygenation and since 2005 all RCTs published have used longer duration of prone ventilation. Prone ventilation even reduces incidence of ventilator-associated pneumonia (VAP) as has been seen in few studies.

Methodology

Proning should be started in ARDS of greater than 24 hours duration, generally on the second day. The frequency is usually once a day with duration of proning varying from 4–20 hours as shown by different studies. Timing, usually ARDS more than 24 hours/2nd day. Prone position may be achieved by:

- Manually positioning the patient
- CircOlectric bed (used in late 1970s)
- Chains and pulley system
- Light weight portable support frame (Vollman prone positioner).

Cushions or gel pads are required to prevent bedsores at pressure points. Three to five persons are generally required to put a patient in prone position. The abdomen is allowed to protrude and the head position is down. Patient will require sedation and neuromuscular blocking agents.

CONTRAINDICATIONS

Contraindications to Prone Positioning

- Life-threatening circulatory shock
- Spinal instability
- Pelvic fractures
- Increased intracranial pressure (ICP)
- Burns or open wounds on the face or ventral body surface
- Active intra-abdominal pathology.

Complications

- Pressure ulcers
- Airway obstruction
- Unplanned extubation or endotracheal tube dislodgement
- Unplanned removal of central venous, arterial or pulmonary arterial catheters
- Thoracotomy tube dislodgement
- Pneumothorax
- Facial and periorbital edema
- Hypotension, arrhythmias
- Vomiting.

A recent large French trial (Proseva study) has demonstrated that early application of prolonged prone-positioning sessions (at least 16 hours) in severe ARDS significantly decrease 28-day and 90-day mortality. They proned the patients for at least 16 hours before making them supine for 4 hours and this strategy was applied every day up to 28 days depending on physician's discretion.

HIGH FREQUENCY OSCILLATORY VENTILATION

It is characterized by rapid oscillations of a reciprocating diaphragm, leading to high respiratory cycle frequencies, usually between 3 Hz and 9 Hz in adults, and very low tidal volume (VT). The ventilation in high frequency oscillatory ventilation (HFOV) is primarily achieved by oscillations of the air around the set mean airway pressure (mPaw). The volume swing is minimized. The goal of HFOV is to oxygenate and ventilate the lung without VILI. Conceptually, it is very attractive, as it achieves many of the goals of lung-protective ventilation:

- *mPaw*: Maintains an "open lung" and optimizes lung recruitment
- Lower VT than controlled ventilation (CV), thus theoretically avoiding alveolar distension.
- *Expiration is active*: Prevents gas trapping
- *Higher mPaws (compared to CV)*: Leads to higher end-expiratory lung volumes and recruitment, leads to improvements in oxygenation and, in turn, decrease in FiO_2.

The pressure-time graph depicting HFOV tracing in comparison to conventional mechanical ventilation (CMV) (Fig. 2).

INDICATIONS OF HFOV

- ALI/ARDS (adults)
- Neonatal indications
- Air leaks—pneumothorax, pulmonary interstitial empyema.

The important point to remember is that most of the studies done with HFOV in ARDS are prospective,

by mansdocs.com

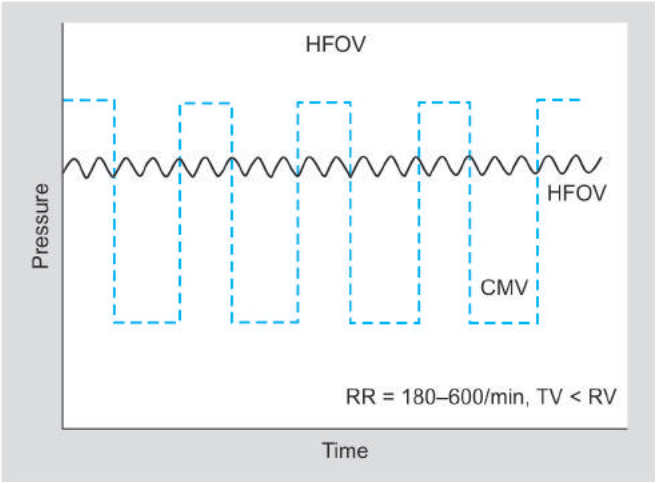


Fig. 2: Comparison of CMV and HFOV
(CMV: Conventional mechanical ventilation; HFOV: High frequency oscillatory ventilation; RR: Respiratory rate; RV: Residual volume, TV: Tidal volume).

observational and retrospective. Only two RCTs have been published so far comparing HFOV with CMV. In these studies, it was shown that it may improve oxygenation when used as a rescue modality in adult patients with severe ARDS failing conventional ventilation. The 30-day mortality in these two RCTs was found to be less in patients treated with HFOV but was not significant in comparison with CMV. This has been shown below:

- Derdak et al.—148 pts—HFOV 37%/CMV 52% (P = 0.10)
- Bollen et al.—61 pts—HFOV 43%/CMV 33% (P = 0.59)—trial stopped early due to severe methodological problems.

HFOV may be considered for patients with severe ARDS:

- FiO_2 > 0.60 and/or SpO_2 < 88% on CMV with positive end-expiratory pressure (PEEP) > 15 cm H_2O,
- Plateau pressures (Pplat) > 30 cm H_2O,
- mPaw ≥ 24 cm H_2O
- Airway pressure release ventilation Phigh ≥ 35 cm H_2O.

CONTRAINDICATIONS

Relative contraindications are:

- Raised intracranial pressure (ICP)
- Obstructive lung disease.

LIMITATIONS AND PITFALLS

Potential limitations and pitfalls are:

- Barotrauma—due to high mPaw
- Hemodynamic compromise.
- Requires heavy sedation and frequent paralysis and this may prolong duration of mechanical ventilation, and can increase ICU and hospital length of stay. Recent two major trials on the use of HFOV in ARDS patients have not shown any outcome benefit and have suggested that it may in fact increase in-hospital mortality.

BIBLIOGRAPHY

1. Abroug F, Ouanes-Besbes L, Elatrous S, et al. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendation for research. Intensive Care Med. 2008;34(6):1002-11.
2. Bollen CW, van Well GTJ, Sherry T, et al. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syn-drome: a randomized controlled trial [ISRCTN24242669]. Crit Care. 2005;9(4):R430-9.
3. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis. 1974;110(6 Pt 2):143-4.
4. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med. 2002;166(6):801-8.
5. Ferguson ND, Cook DJ, Guyatt GH et al. High-frequency oscillation in early acute respiratory distress syndrome. N Eng J Med 2013;368:795-805.
6. Galiatsou E, Kostanti E, Svarna E, et al. Prone position augments recruitment and prevents overinflation in acute lung injury. Am J Respir Crit Care Med. 2006;174(2):187-97.
7. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Eng J Med 2013;368:2159-68.
8. Higgins J, Estetter B, Holland D, et al. High-frequency oscillatory ventilation in adults: respiratory therapy issues. Crit Care Med. 2005;33(3 Suppl):S196-203.
9. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010;36(4):585-99.
10. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2009; 302(18):1977-84.
11. Young D, Lamb SE, Shah S et al. High-frequency oscillation for acute respiratory distress syndrome. N Eng J Med 2013;368:806-13.

by mansdocs.com

CHAPTER 81

Extracorporeal Membrane Oxygenation

Rajesh Pande, Vivek Gupta, Abhishek Vishnu

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) used to be expensive, cumbersome, difficult to manage, limited to specialized and dedicated centers (children's hospitals). But the new generation ECMO is much simpler, safer, less complicated and easier to manage in any ICU. The recent enthusiasm in ECMOs because of the advances that have been made in the technology which include the new low resistance, high flow hollow membrane lung, centrifugal pumps, less thrombogenic circuits with a longer life, increased reliability, and reduction in the incidence of device-related adverse events. The new generation ECMO can be handled by the trained ICU nurse. The limitation to widespread application the need for anticoagulation and bleeding complications. It is believed that the future will bring routine applications of ECMO to all advanced ICUs where profound respiratory and cardiac failures are treated.

Extracorporeal membrane oxygenation takes over the function of lungs and/or heart for patient diseases that are "reversible" without ECMO. It allows lungs to be "rested". Blood is removed from the venous system either peripherally via cannulation of a femoral vein or centrally via cannulation of the right atrium, blood is warmed and oxygenated, excess CO_2 is removed and oxygenated blood is then returned back to the body-in V-A ECMO, via a femoral artery/aorta and in the V-V ECMO, via the right atrium (Figs. 1 and 2).

Neonatal ECMO is applied in the following conditions:

- Neonate is more than 33 weeks gestation (weight > 2 kg)
- Reversible pulmonary disease
  - Meconium aspiration
  - Idiopathic respiratory distress syndrome
  - Sepsis with pneumonia
  - PPHN
  - CDH
- Predicted mortality of at least 80%.

EXCLUSION CRITERIA FOR NEONATAL ECMO

- Major chromosomal anomalies incompatible with reasonable outcome.
- Major cardiac or CNS malformations.
- Intracranial hemorrhage more than Grade 1.
- Ventilator support more than 10 days.
- Uncontrolled bleeding.
- Irreversible disease process.

TYPES OF ECMO

- Veno-venous ECMO (VV ECMO) (Figs. 3 and 4)
- Veno arterial ECMO (VA ECMO)
- Extracorporeal CO_2 removal—uses a smaller cannula with blood flow adequate to just remove CO_2. It removes CO_2 using a pumpless circuit, with flows driven by patient's own pressure.

Indications of Adult ECMO

The indications of ECMO are as follows:

- Duration of mechanical ventilation less than 5–7 days
- Pulmonary compliance less than 0.5 mL/cm H_2O/kg

by mansdocs.com

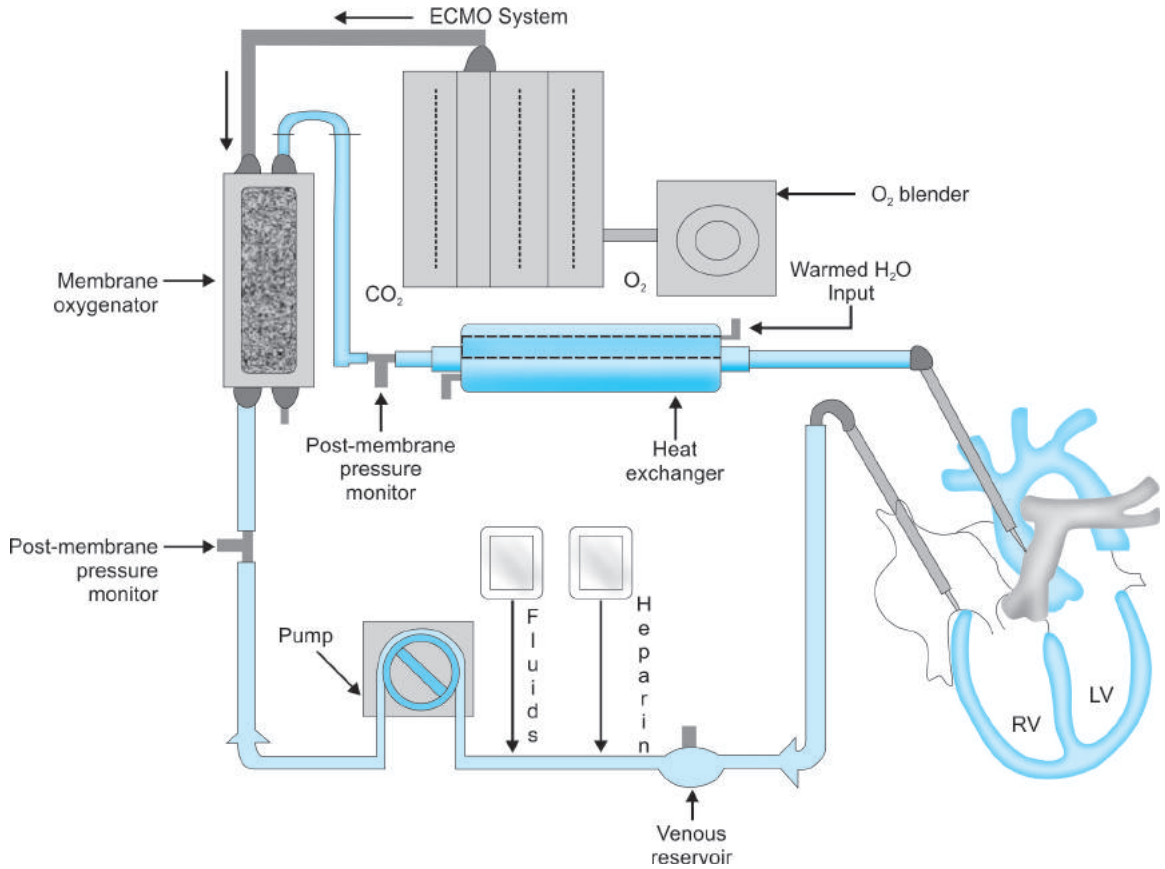


Fig. 1: Extracorporeal membrane oxygenation (ECMO) circuit.

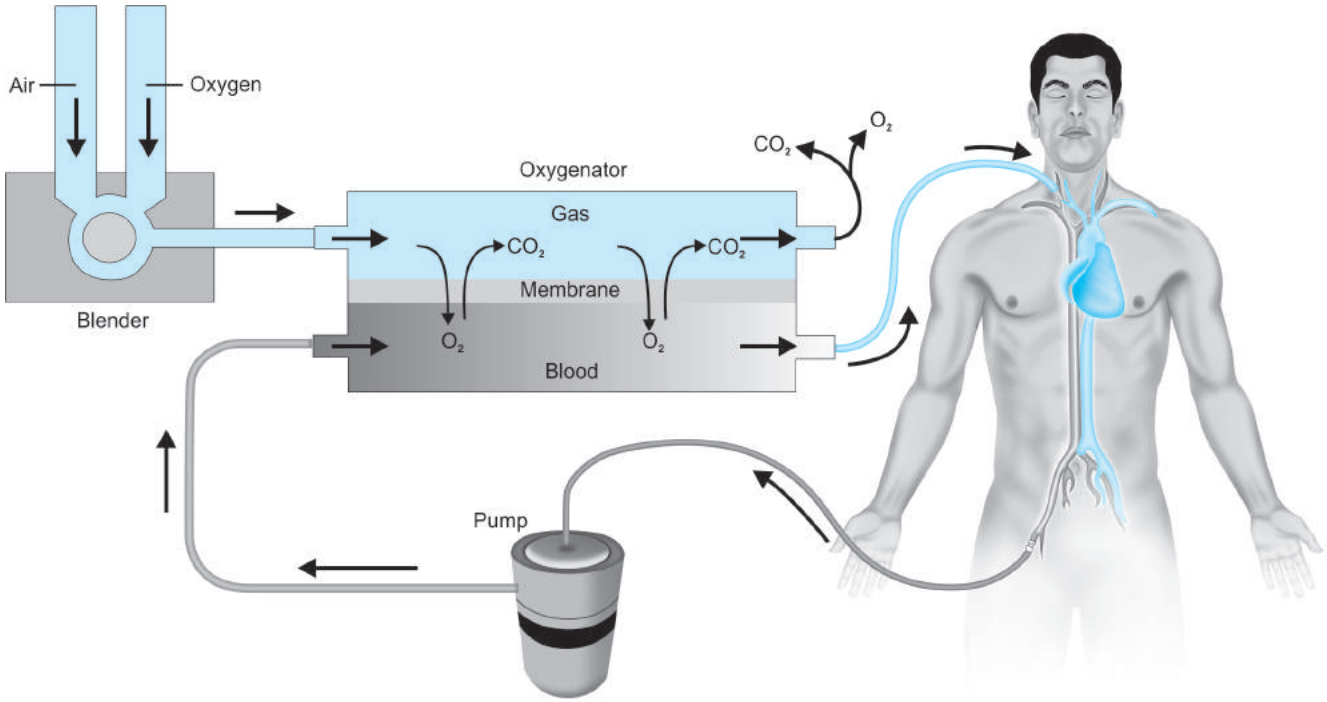


Fig. 2: The dynamics of extracorporeal membrane oxygenation.

by mansdocs.com

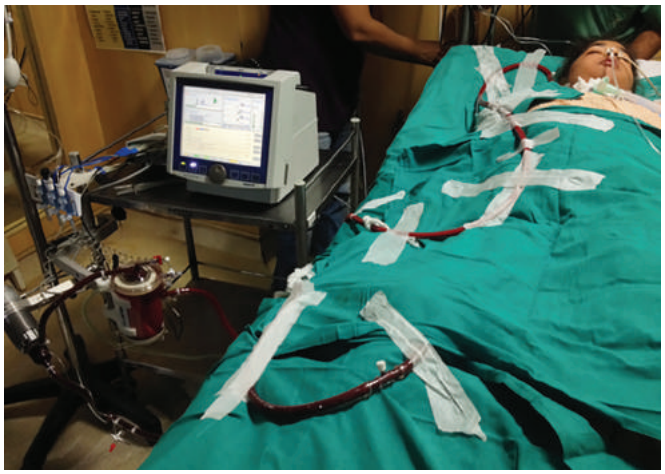


Fig. 3: Veno-venous extracorporeal membrane oxygenation.



Fig. 4: Veno-venous extracorporeal membrane oxygenation.

- PaO_2/FiO_2 ratios less than 100 and no response to standard therapies for severe acute respiratory distress syndrome (ARDS) , or shunt more than 30%.

Contraindications

There is no absolute contraindication to ECMO. Relative contraindications include:

- Mechanical ventilation with a high setting FiO_2 more than 0.9
- Plateau pressure more than 30 for more than or equal to 7 days
- Major pharmacological immunosuppression (Neutrophils count less than 400 cells/mm^3)
- Recent or expanding CNS hemorrhage
- Contraindication to systemic anticoagulation.

Probably the future will bring routine applications of ECMO to all advanced ICUs.

Traditional cannulation for veno-venous ECMO has been a two cannulae system—venous drainage from the right femoral vein and return to the right atrium via a right internal jugular vein cannula. A single bicaval dual lumen cannula placed in the internal jugular position is now available. This is placed percutaneously in the right internal jugular vein and allows simultaneous removal of blood from the superior and inferior vena cavae with return of blood into the right atrium with minimal recirculation.

STARTING ECMO

Steps in Starting ECMO

- Preparation of the patient
- Pump and circuit assembly and priming
- Cannulation
- Connecting the ECMO circuit
- Running the ECMO
- Adjusting ventilation parameters
- Daily management
- Weaning

Adjustments during ECMO

Sweep Gas

It is fresh gas supplied by the blender and is delivered to the gas side of the oxygenator and allows for exchange of O_2 and CO_2 with the extracorporeal blood. The term used for sweep gas is FDO_2 (not FiO_2)—fraction of delivered oxygen. The CO_2 is controlled by the flow rate of sweep gas. The oxygenation is modulated by altering the blood flowing through the ECMO circuit (limited by size of drainage cannula).

Anticoagulation

Systemic anticoagulation is achieved with unfractionated heparin. Initial bolus is given before cannula insertion and subsequently the APTT is maintained between 40–60 seconds. However, the target range varies from center to center. The activated clotting time (ACT) may be monitored and kept between 180–220 seconds.

Ventilatory Setting

There are no set guidelines or protocols. The protective lung strategy is followed, limiting the peak inspiratory pressure (PIP) to 20–25 cm H_2O. The frequency is 10/min PEEP 10–15 cm H_2O, FiO_2 of 0.3. The tidal volume (VT) can

by mansdocs.com

be even maintained below 4 mL/kg. After improvement patient may be weaned to pressure support ventilation.

Aggressive Diuresis

Aggressive diuresis is attempted whenever possible. If required, use an ultrafiltration to facilitate a conservative fluid approach. If extracorporeal blood flow is compromised by depletion of intravascular volume, do not infuse more fluids, rather reduce pump flow. An increase in FiO_2 on ventilator temporarily may be required. Reverse changes once intravascular volume is restored from extravascular space.

Transfusion Triggers

There are no set guidelines. The New England Journal paper recommends same triggers as for ARDS patients. Platelets should be more than 20,000 or above 50,000 if active bleeding is occurring.

Weaning from ECMO

- Reduce sweep gas flow and FDO_2 and blood flow. The ventilator requirements are less-FiO_2 less than 60%, pressures less than 30 cm H_2O. Ventilation can be switched over to pressure support later.
- Confirm catheter placement (CXR and Echo) for venous cannula in the right atrium and the arterial cannula in the ascending aorta.
- *Prime pump*: Circulate with CO_2 followed by crystalloid and 5% albumin then 2 units PRBC's.
- *Oxygenator*: Both O_2 and CO_2 exchanged. Can form thrombus over time.
- *Fluid management*: Patients often gain weight in the first 1–3 days and then diuresis starts.
- *The "Rest Settings" on ventilator*: 20–25/5 × 12, 0.40, $T_i = 0.5$.
- Other critical care issues include management of blood pressure, nutrition, seizures, etc.
- Anticoagulation is achieved by Heparin 50–100 mg/kg bolus followed by 30–60 mg/kg/hr continuous infusion. The clotting should be monitored by activated clotting time (ACT) with a goal of is 180–220 seconds.

CESAR Trial

A multicenter, prospective, randomized (n = 180) that included severe potentially reversible acute respiratory failure defined as Murray score more than 3 and a pH less than 7.20. The exclusion criteria included high pressure more than 30 (PIP), high FiO_2 more than 0.8 and patients on ventilator for more than 7 days. The primary outcome was death/severe disability, 6 months after randomization/or before discharge from the hospital.

Patients were randomly allocated to treatment by an algorithm that could include ECMO or conventional management. For ECMO, patients were shifted to Leicester ECMO Center. In the control group (n = 90), 41 patients survived and 6 month survival was 47%, whereas in the study group (n = 90), 5 patients died before/during transport, 17 improved and ECMO was required in 68 patients in whom the 6 month survival was 63%.

The study was stopped by Data Safety Monitoring Board for effectiveness after 180 patients. The study concluded that management of ARDS with standard algorithm including ECMO in an expert care center resulted in better survival than best care in other centers.

PARTIAL ECMO SUPPORT—EXTRACORPOREAL CO_2 REMOVAL

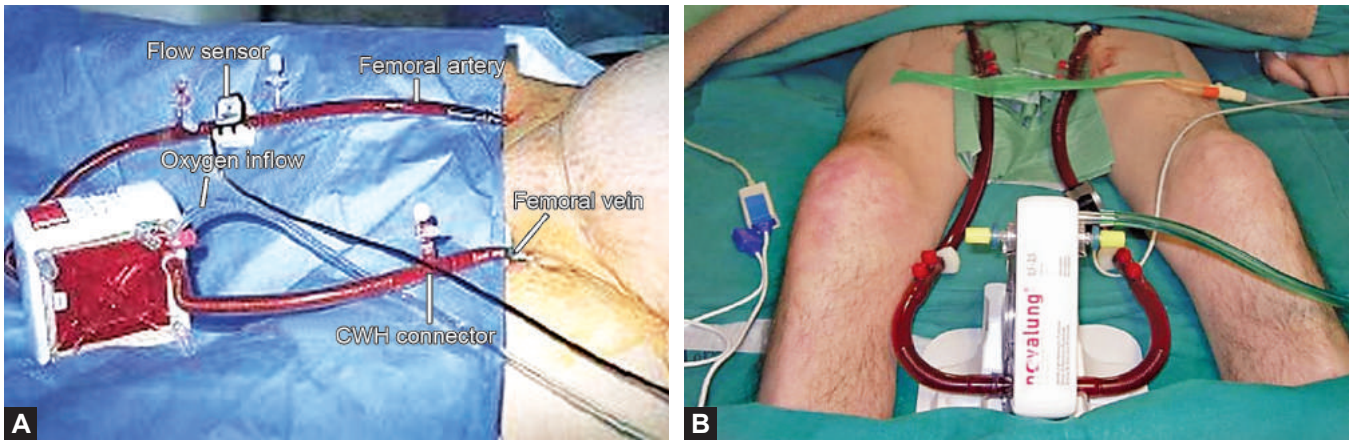
Acute respiratory distress syndrome patients are exposed to VILI despite low VT ventilation (1/3 of patients). The high $PaCO_2$ and low pH may limit the application of low VT ventilation. We can combine CO_2 removal with protective lung ventilation to protect the lung by further reducing VT, manage acidosis with minimal or no side effects. A veno-venous system can be used for this purpose.

NOVALUNG INTERVENTIONAL LUNG ASSIST (AV PUMP-LESS ECMO)

The Novalung Interventional Lung Assist (iLA) device is a membrane ventilator that allows for oxygen and carbon dioxide gas exchange to occur by simple diffusion (Figs. 5A and B). It has been used in patients with severe acute lung failure due to ARDS, inhalation injury, severe pneumonia, chest injury, foreign body aspiration, and after thoracic surgical interventions. The advantages are: simple, does not require a pump, small priming volume, no mechanical damage to the blood components, no recirculation. However, the disadvantages may be: no direct blood flow control, left to right shunt, etc. The primary function of this pump less arteriovenous system is to facilitate CO_2 exchange.

Novalung has been used as bridge to lung transplant in patients with end-stage lung disease and respiratory failure. While waiting for the lung transplant, patient may be assisted with a CPAP in spontaneous breathing and the CO_2 removal device with very good gases exchange.

by mansdocs.com



Figs. 5A and B: Novalung AV pump-less ECMO.

BIBLIOGRAPHY

1. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009;302(17):1888-95.
2. N Engl J Med 2009;361:1–10
3. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374(9698):1351-63.

by mansdocs.com

CHAPTER

82

Aerosol Delivery Systems in Mechanical Ventilation

Rajesh Pande, Pritpal Kaur

The goals of aerosol delivery are high efficiency of aerosol delivery, reproducible dosing, targeted delivery to the site of action, short duration of treatment, and ease of device operation. It should be cost effective, environment friendly with minimal risk to the patient and the clinician.

The common conditions for which inhaled therapies are given to adult intensive care unit (ICU) patients: include surfactant and anti-inflammatory therapy in acute respiratory distress syndrome (ARDS), antibiotics in pneumonia and sepsis, bronchodilators and anti-inflammatory therapy in chronic obstructive pulmonary disease (COPD) exacerbations and asthma, vasodilators in pulmonary hypertension.

The factors controlling drug delivery to the lungs:

- Physical characteristics of the aerosol particle
  - Size
  - Density
  - Electrical charge
  - Hygroscopy
  - Shape
  - Velocity of the aerosol particle
- Host factors
  - Inspired volume
  - Inspiratory time
  - Inspiratory flow
  - Breath hold duration
  - Timing of aerosol delivery during inspiration [with metered dose inhalers (MDI)].

THE MECHANISM OF AEROSOL DELIVERY

Inertial impact: The large particles (>3 U) are deposited in proximal airways.

Sedimentation: Particles rain out under effect of gravity and the suspended particles rain out slowly. Smaller particles remain suspended for longer and are likely to be exhaled out, but have more chances of reaching distal airways.

Diffusion: Due to Brownian movement particles collide with airway wall (<0.5 U).

AEROSOL THERAPY DURING MECHANICAL VENTILATION

- Pressurized metered dose inhalers (pMDIs)
- Nebulizers.

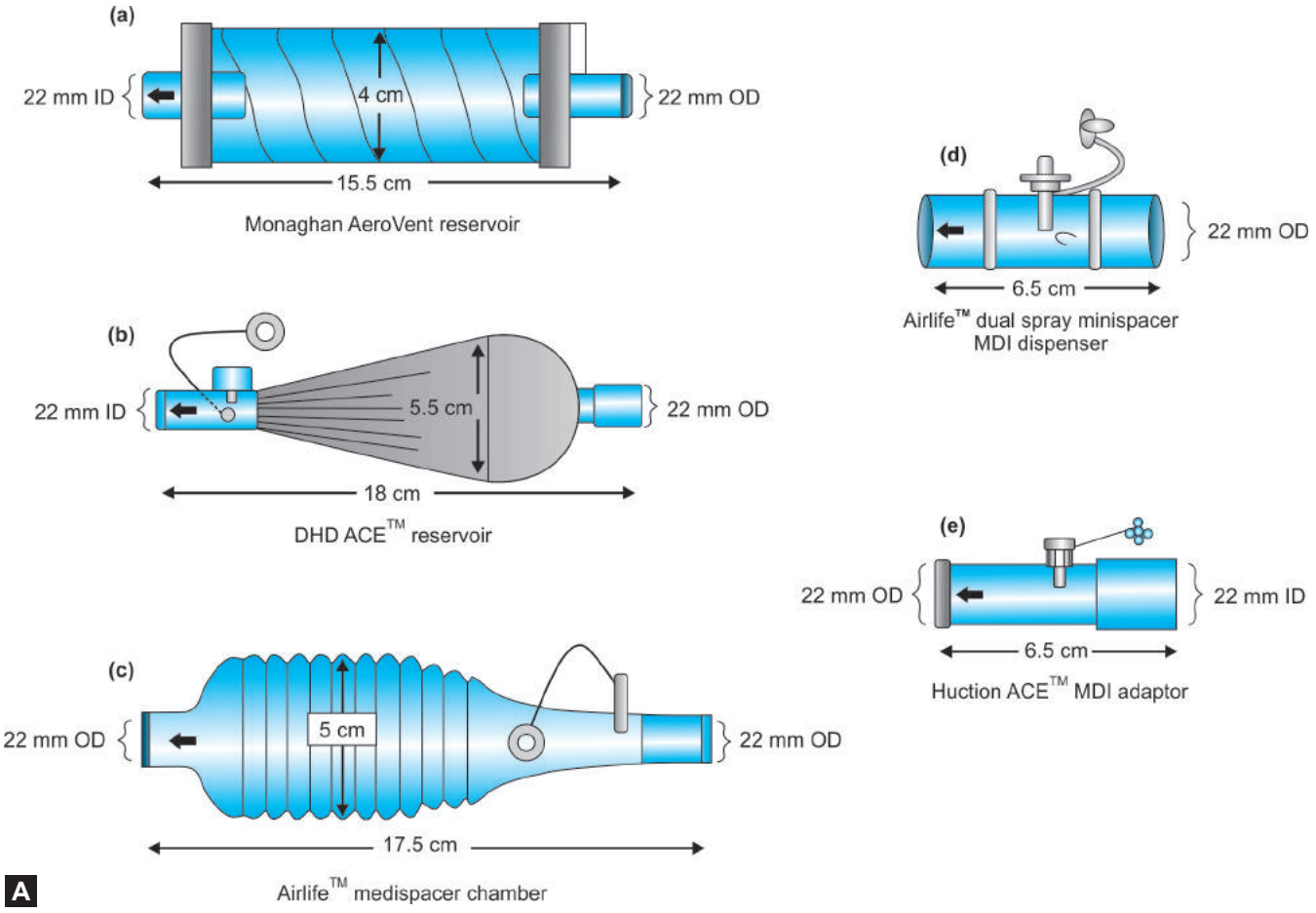
Older generation: Wide variation in performance: pMDIs: 0.3–97.5%, nebulizers: 0–42%.

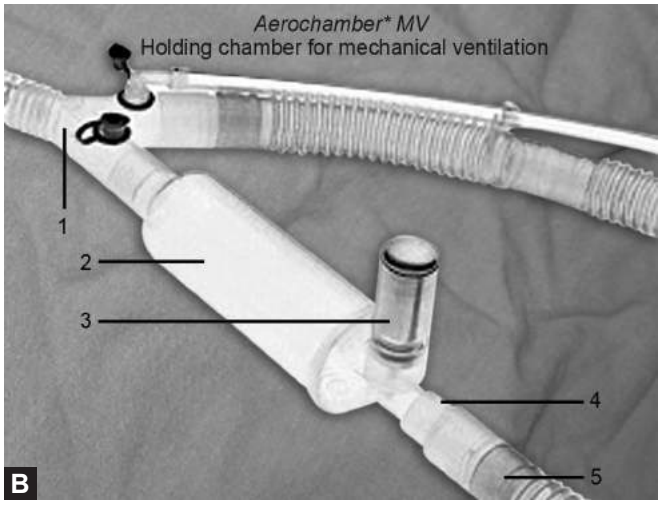
Pressurized metered dose inhalers: Used to deliver beta-adrenergic and anticholinergic bronchodilators for airway obstruction.

SPACER OR ADAPTER DEVICES (FIGS. 1A AND B)

- *Devices*: Elbow adapters, inline devices (unidirectional/bidirectional) and chamber or reservoir adapter.

by mansdocs.com

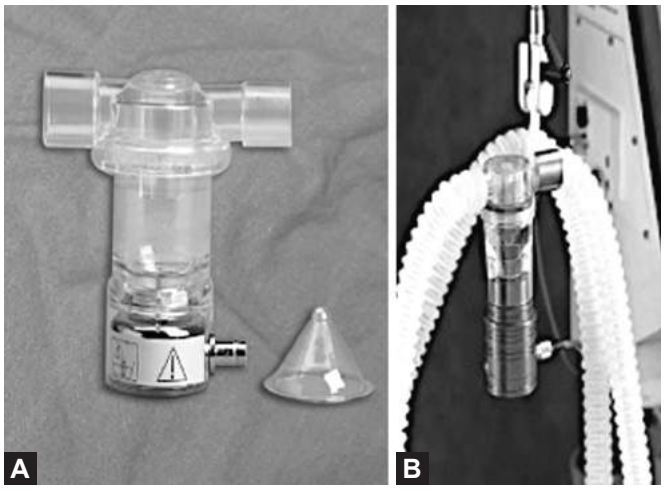




Figs. 1A and B: (A) Various aerosol delivery systems; (B) Aerochamber.

- A chamber spacer with pMDIs in ventilator circuit results in 4–6 fold greater aerosol delivery compared with elbow adapter or a unidirectional inline spacer.
- A pMDI and chamber spacer placed at 15 cm from the endotracheal tube (ET) tube provide efficient aerosol delivery with significant bronchodilator response.

by mansdocs.com



Figs. 2A and B: (A) Servo Ultra nebulizer 345 series; (B) Easy Neb US nebulizer for PB 700 and 800



Fig. 3: Aeroneb vibrating mesh nebulizer

AEROSOL DELIVERY SYSTEMS

Jet Nebulizers

Here a jet of oxygen or compressed air is used to generate the aerosol. The jet nebulizer is connected to the inspiratory limb and can be pressurized by external oxygen/air or using a separate line from ventilator to generate flow and pressure. Intermittent operation is more efficient than continuous aerosol generation. Ventilators with inbuilt nebulizers are better as they deliver reproducible and consistent dosing. Placing nebulizer at a distance from ET is better than keeping it between ETT and Y piece. Addition of reservoir increases delivery.

Ultrasonic Nebulizers (Figs. 2A and B)

The vibration frequency and amplitude of vibration of the piezoelectric crystal influence aerosol particle size and drug output. The drug solution becomes more concentrated during operation and the solution temperature increases by 10–15°C after a few minutes. The aerosol particle size is larger with ultrasonic nebulizers compared to jet nebulizers. Ultrasonic nebulizers have a higher efficiency for aerosol delivery during mechanical ventilation than jet nebulizers. The cost and bulk, and their relative inefficiency in nebulizing drug suspensions are major limitations to their use.

Placing US nebulizer proximal or distal to Y piece does not influence the efficiency of aerosol delivery. Placing it in inspiratory limb 50 cm from Y piece does not improve its efficacy. But addition of cylindrical storage chamber

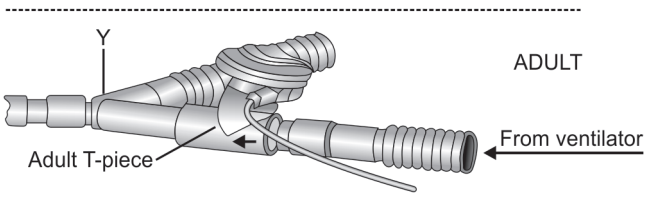


Fig. 4: Vibrating mesh nebulizer attached to breathing circuit

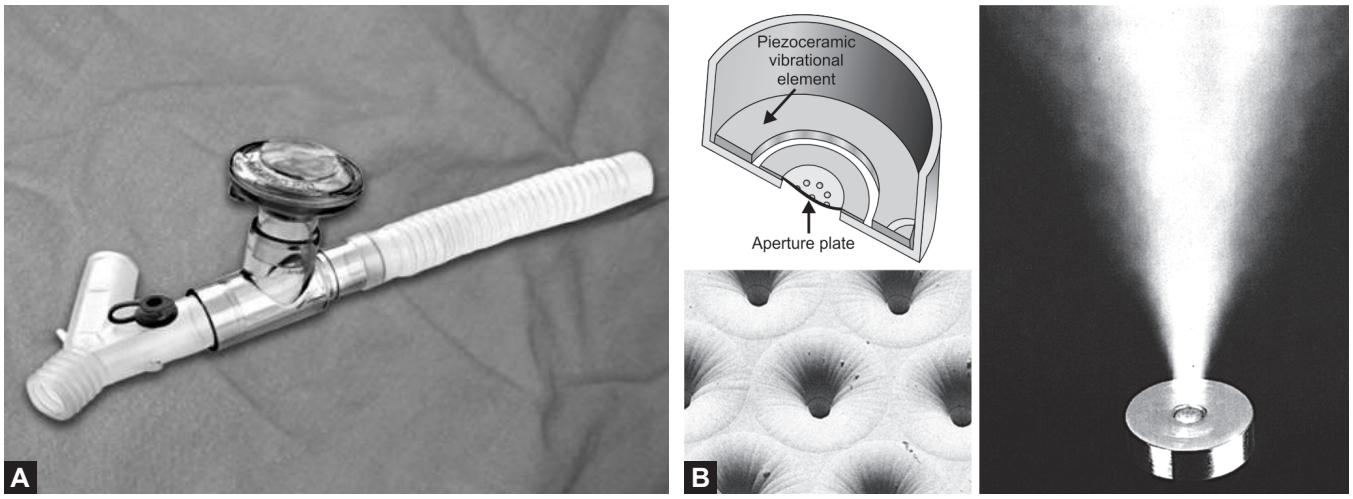
(500–600 mL) doubles the efficiency of aerosol delivery with US nebulizers. Efficiency can be increased by longer inspiratory time, reducing minute ventilation, lowering respiratory rate.

High efficiency devices: These deliver a high proportion of the drug to the lungs with minimum wastage. Precision and consistency of dosing depends on: device, administration technique, ventilator settings and presence of patient-related factors and severity of airway disease.

AEROSOL DEVICE: VIBRATING PLATES (FIGS. 3 TO 5)

These devices use a vibrating mesh or plate with multiple apertures to produce a liquid aerosol. Examples are: Aerogun, Omron, ODEM, and PARI Respiratory Equipment. They generate aerosols with a high fine-particle fraction and their efficiency of delivering drugs to the respiratory tract is higher than conventional jet or ultrasonic nebulizers. The aerosol is generated as a fine mist and no internal baffling system is required. These devices are portable, battery operated (operation with alternating current is

by mansdocs.com



Figs. 5A and B: Aeroneb nebulizer connected to the ventilator circuit; (B) Vibrating plate with multiple apertures delivering a fine aerosol spray

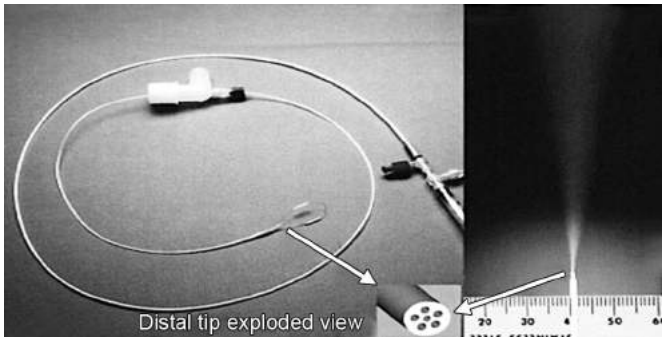


Fig. 6: Aero probe catheter

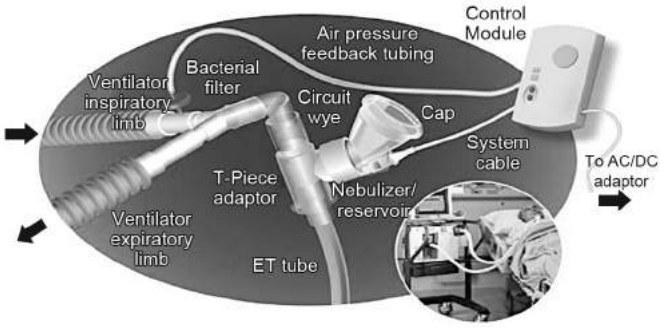


Fig. 7: Pulmonary drug delivery system for ventilated patients

optional with some); they efficiently aerosolize solutions and suspensions, and they have minimal residual volume of medication left in the device. Some are breath-actuated, thereby limiting release of aerosolized drug into the ambient air.

Tiny multi-lumen catheter is designed to fit in the suction channel of the bronchoscope. It allows for generation of intrapulmonary aerosol at the tip of the bronchoscope.

AERO PROBE (FIG. 6)

The extracorporeal nebulizing catheter produces an aerosol in the trachea. A central lumen transmits the solution to be nebulizer and compressed gas is forced under high pressure (100 psi) at a variable flow rate (0.1–3.0 L/min) through several additional lumens that surround the central lumen. Droplets of drug solution form at the tip of the catheter and aerosol is formed by the pressurized gas breaking up the liquid droplets. The catheter produces an aerosol continuously or intermittently when a pulsed gas flow is employed. The pressure and flow rate of the gas determine the aerosol particle size. Lung deposition is improved with the use of the catheter compared to more conventional forms of aerosol administration. It holds considerable promise as a means of targeting inhalational delivery of a variety of therapeutic agents and genes in ventilated patients to the site of disease in the lung.

PULMONARY DRUG DELIVERY SYSTEMS (FIGS. 7 AND 8)

Breath synchronized version of Aeroneb Pro (Pulmonary drug delivery systems): It is microprocessor driven and uses a pressure transducer to monitor changes in airway pressure and identify the inspiratory time. Aerosol is delivered only during specified portion of inspiratory time.

by mansdocs.com

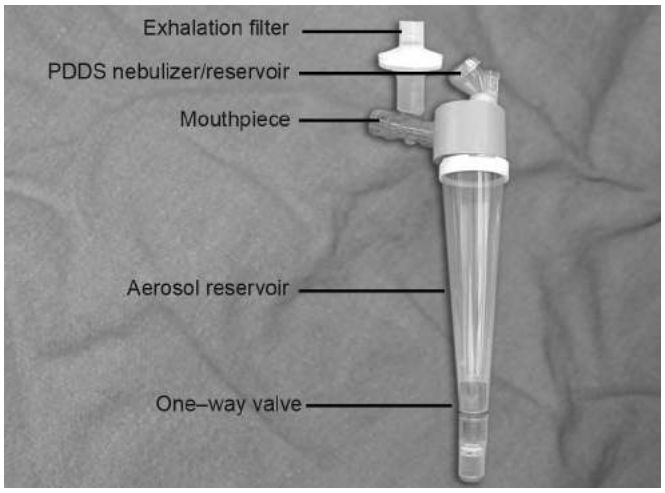


Fig. 8: Pulmonary drug delivery system for extubated patients

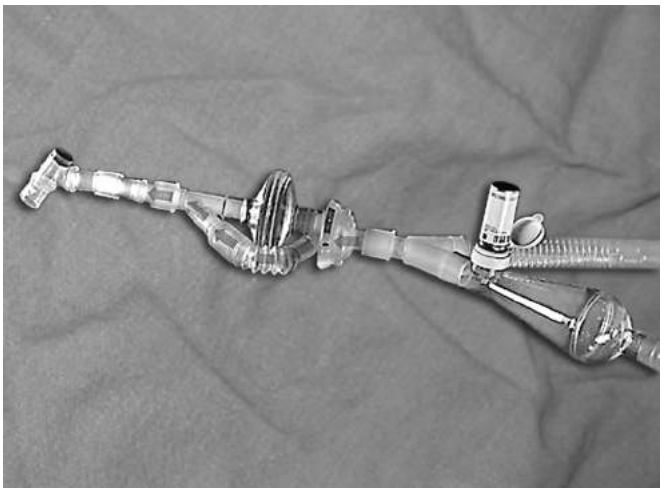


Fig. 9: Drug delivery by metered dose inhalers with reservoir in ventilated patient

Pulmonary drug delivery system ensures a very good delivery in alveolar epithelial lining fluid. A similar device is available for extubated patients also. A similar device is also available for extubated patients.

Factors influencing aerosol delivery in mechanically ventilated patients.

- *Ventilator related*:
  - Ventilation mode
  - Tidal volume
  - Respiratory rate
  - Duty cycle
  - Inspiratory waveform
  - Breath triggering mechanism
- Device related (MDI)
  - Type of spacer or inhaler
  - Position of spacer in circuit
  - Timing of MDI actuation
  - Type of MDI
- Device related nebulizer
  - Type of nebulizer
  - Fill volume
  - Gas flow
  - Cycling-Intermittent versus continuous
  - Duration of nebulization
  - Position of nebulizer in circuit
- Circuit related
  - Endotracheal tube size
  - Humidity of inhaled gas
  - Density of inhaled gas
- Drug related
  - Dose
  - Formulation
  - Aerosol particle size
  - Targeted site for delivery
  - Duration of action
- Patient related
  - Severity of airway obstruction
  - Mechanism of airway obstruction
  - Presence of dynamic hyperinflation
  - Patient ventilator synchrony

Technique for Drug Delivery by MDI in Ventilated Patients (Fig. 9)

- Review order, identify patient and assess need for bronchodilator
- Suction ETT and airway secretions
- Shake MDI and warm to hand temperature
- Place pMDI in space chamber adapter in ventilatory circuit
- Remove heat and moisture exchangers (HME). Do not disconnect humidifier
- Coordinate pMDI actuation with beginning of inspiration
- Wait at least 15 seconds between actuations, administer total dose
- Monitor for adverse response
- Reconnect HME
- Document clinical outcome.

Technique for Drug Delivery by Jet Nebulizer in Ventilated Patients

- Review order, identify patient and assess need for bronchodilator

by mansdocs.com

- Suction ETT and airway secretions
- Place drug in nebulizer to fill 4–6 mL volume
- Place nebulizer in inspiratory limb 18 inches from patient Wye connector
- Turn off flow or continuous flow during nebulizer operation
- Remove HME. Do not disconnect humidifier
- Set nebulizer gas flow 6–8 L/min
- Adjust ventilator volume or pressure to adjust for additional flow
- Tap nebulizer periodically until nebulizer begins to sputter
- Remove nebulizer from circuit, rinse with sterile water, safe dry and store
- Reconnect HME
- Assess outcome and document clinical outcome.

It has been shown that the position of the nebulizer in the ventilatory circuit has no effect on the pulmonary bioavailability of bronchodilator.

SIGNIFICANT DIFFERENCE IN HUMIDIFIERS VERSUS NON-HUMIDIFIERS AEROSOL DELIVERY DURING NONINVASIVE VENTILATION

Conventional nebulizers may not provide optimal delivery and aerosol delivery can vary from 5–25% depending on inspiratory and expiratory pressures and synchronization of pMDIs actuation with inhalation. pMDIs may deliver aerosol with a chamber spacer and face mask or nebulizer and face mask.

To summarize, aerosol delivery may be quite variable during mechanical ventilation. Mechanical ventilator modes, flows, and flow patterns may affect particle deposition. The presence of an in-line humidifier may reduce aerosol delivery by 50%. Vibrating mesh nebulizers are the most efficient, least affected by other conditions.

Breath actuators may increase delivery significantly compared to the continuous flow.

BIBLIOGRAPHY

1. Ari A, Atalay OT, Harwood R, et al. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. Respir Care. 2010; 55:845-51.
2. Dhand R. Aerosol delivery during mechanical ventilation: from basic techniques to new devices. J Aerosol Med Pulm Drug Deliv. 2008; 21:45-60.
3. Dhand R. Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. Respir Care. 2005; 50:1331-4
5. Dolovich M. Changing delivery method for obstructive lung diseases. Curr Opin Pulm Med 1997;3(3):177-89.
4. Duarte A. Inhaled Bronchodilator administration during mechanical ventilation. Respire Care. 2004;49:6.
6. MacLoughlin RJ , Dip H, Higgins BD et al. Optimized aerosol delivery to a mechanically ventilated rodent. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2009;22: 323–32.

by mansdocs.com

APPENDICES

Appendix 1: Hemodynamic Formulae and Values

Pressure = Flow × Resistance

Cardiac Output

$$\text{Output of left ventricle} = \frac{O_2 \text{ consumption (mL/min)}}{[AO_2]-[VO_2]}$$

By thermodilution,

$$Q = \frac{V(T_b - T_t)K}{\int T_b(t)\,dt}$$

Q = Cardiac output
V = Volume of injectate
T_b = Blood temperature
T_i = Injectate temperature
K = A constant including the density factor and catheter characteristics
$\int T_b(t)dt$ = Area under the blood-temperature-time curve

For pulmonary blood flow,

$$Q = \frac{VO_2}{(CaO_2 - CvO_2)}$$

where

Q = Total pulmonary blood flow
VO_2 = Oxygen uptake
CaO_2 = Arterial oxygen concentration
CvO_2 = Venous oxygen content equation

Normal Hemodynamic Parameters: Equations and Normal Range

- Arterial blood pressure (BP)
- Systolic blood pressure (SBP): < 120 mm Hg
- Diastolic blood pressure (DBP): < 80 mm Hg
- Mean arterial pressure (MAP) = [SBP + (2 × DBP)]/3: 70–105 mm Hg
- Right atrial pressure (RAP): 2–6 mm Hg
- Right ventricular pressure (RVP)
- Right ventricular systolic pressure (RVSP): 15–25 mm Hg
- Right ventricular diastolic pressure (RVDP): 0–8 mm Hg
- Pulmonary artery pressure (PAP)
- Pulmonary artery systolic pressure (PASP): 15–25 mm Hg
- Pulmonary artery diastolic pressure (PADP): 8–15 mm Hg
- Mean pulmonary artery pressure (MPAP) = [PASP + (2 × PADP)]/3: 10–20 mm Hg
- Pulmonary artery wedge pressure (PAWP): 6–12 mm Hg
- Left atrial pressure (LAP): 6–12 mm Hg
- Cardiac output (CO) = heart rate (HR) × stroke volume (SV)/1,000: 4.0–8.0 L/min
- Cardiac index (CI) = CO/body surface area (BSA): 2.5–4.0 L/min/m^2
- SV = CO/HR × 1,000:60–100 mL/beat
- Stroke volume index (SVI) = CI/HR × 1,000:33–47 mL/m^2/beat
- Systemic vascular resistance (SVR) = 80 × (MAP – RAP)/CO 800: 1,200 dynes/cm^5/m^2
- Systemic vascular resistance index (SVRI) = 80 × (MAP – RAP)/CI: 1,970–2,390 dynes/cm^5/m^2
- Pulmonary vascular resistance (PVR) = 80 × (MPAP – PAWP)/CO: < 250 dynes/cm^5/m^2
- Pulmonary vascular resistance index (PVRI) = 80 × (MPAP – PAWP)/CI: 255–285 dynes/cm^5/m^2
- Left ventricular stroke work (LVSW) = SV × (MAP – PAWP) × 0.0136: 8–10 g/m/m^2
- Left ventricular stroke work index (LVSWI) = SVI × (MAP – PAWP) × 0.0136: 50–62 g/m^2/beat
- Right ventricular stroke work (RVSW) = SV × (MPAP – RAP) × 0.0136: 51–61 g/m/m^2
- Right ventricular stroke work index (RVSWI) = SV × (MPAP – RAP) × 0.0136: 5–10 g/m^2/beat
- Coronary artery perfusion pressure (CPP) = Diastolic (BP – PAWP): 60–80 mm Hg

by mansdocs.com

- Right ventricular end-diastolic volume (RVEDV) = SV/EF: 100–160 mL
- Right ventricular end-systolic volume (RVESV) = EDV–SV: 50–100 mL
- Right ventricular ejection fraction (RVEF) = SV/EDV: 40–60%
- Arteriovenous oxygen content difference [$avDO_2$]: This is the difference between the arterial oxygen content (CaO_2) and the venous oxygen content (CvO_2). BSA: Calculated from height and weight, it is generally used to index measured and derived values according to the size of the patient.
- LVSWI: It is the product of the stroke index (SI) and [MAP – pulmonary artery occlusion pressure (PAOP)], and a unit correction factor of 0.0136. The LVSWI measures the work of the left ventricle (LV) as it ejects into the aorta.
- LVSWI = 0.0136´SI (MAP – PAOP)
- MAP: Estimated as one-third of pulse pressure plus the DBP.
- Oxygen consumption (VO_2): Calculated as $C(a - v)O_2 \times CO \times 10$, it is the amount of oxygen extracted in mL/min by the tissue from the arterial blood.
- Oxygen delivery (DO_2): Calculated as $(CaO_2) \times CO \times 10$, it is the total oxygen delivered by the cardiorespiratory systems.
- PVRI: Calculated as (MAP – PAOP)/CI, it measures the resistance in the pulmonary vasculature.
- RVSWI: It is the product of the SI and [MPAP – central venous pressure (CVP)], and a unit correction factor of 0.0136. It measures the work of the right ventricle as it ejects in to the pulmonary artery.
- SI: Calculated as CI/heart rate, it is the average volume of blood ejected by the ventricle with each beat.
- SVRI: Calculated as (MAP – CVP)/CI, it is the customary measure of the resistance in the systemic circuit.
- Venous admixture (Qva/Qt): Calculated as $(CcO_2 – CaO_2)/(CcO_2 – CvO_2)$, it represents the fraction of CO not oxygenated in an idealized lung.

by mansdocs.com

Appendix 2: Respiratory Formulae and Values

- Total lung capacity (TLC): 6 L
- Vital capacity (VC): 4.5 L
- Residual volume (RV): 1.2 L
- Inspiratory capacity (IC): 3 L
- Functional residual capacity (FRC): 3 L
- Inspiratory reserve volume (IRV): 2.5 L
- Expiratory reserve volume (ERV):1.1 L
- Tidal volume (V_T): 0.5 L

  Calculations:

  VC = IRV + ERV + V_T

  RV is difference between the FRC and the ERV: RV = FRC–EV

  Alternatively, if the TLC and VC are known, RV = TLC–VC

  Equilibration:

  V_T: Volume of air inhaled or exhaled with each breath during normal breathing (0.5 L).

  IRV: Maximal volume of air inhaled at the end of a normal inspiration (3 L)

  ERV: Maximal volume of air exhaled at the end of a V_T (1.2 L).

  IC: Maximal volume of air inhaled after a normal expiration (3.6 L) (V_T + IRV)

  FRC: The volume of gas that remains in the lung at the end of a passive expiration (2–2.5 L or 40% of the maximal lung volume) (ERV + RV).

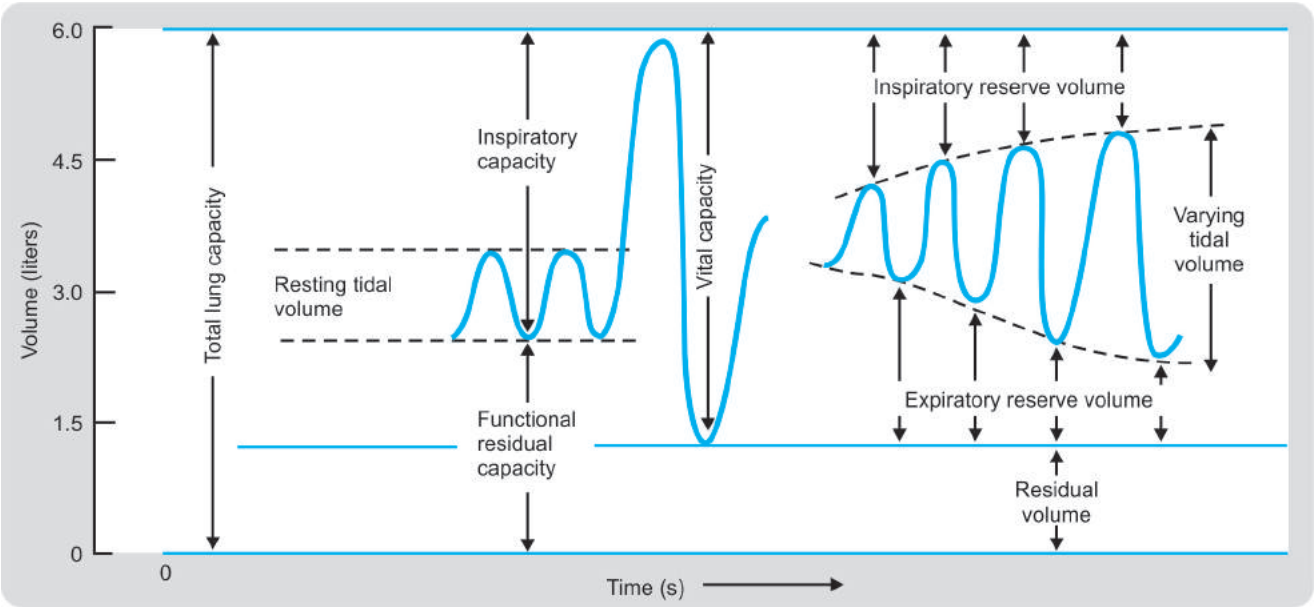
  RV: The volume of gas remains in the lung after maximal expiration (1–1.2 L)

  TLC: The maximal lung volume that can be achieved voluntarily (5–6 L) (IRV + ERV + V_T + RV)

  VC: The volume of air moved between TLC and RV (4–5 L) (IRV + ERV + V_T).

  Multiplying the V_T at rest by the number of breaths per minute gives *the total minute volume* (6 L/min).

  Alveolar ventilation: Volume of fresh gas entering the alveoli per breath alveolar ventilation, VA = VT – VD



by mansdocs.com

Fick's Equation for Oxygen Consumption

Fick Equation

The Fick equation for oxygen consumption (VO_2) is calculated as:

$VO_2 = Q(CaO_2 - CvO_2)$

where

Q = cardiac output (L/min)
CaO_2 = arterial oxygen content
CvO_2 = mixed venous oxygen content

Static Compliance

$$\text{Static compliance } (C_s) = \frac{\Delta V}{\Delta P}$$

Or

$$C_s = \frac{V_T}{\text{Plateau airway pressure} - (\text{PEEP} + \text{auto} - \text{PEEP})}$$

where

V_T = tidal volume
Normal C_s value is 100 mL/cmH_2O/L.

Dynamic Compliance

$$C_{dyn} = \frac{V_T}{\text{Peak airway pressure} - (\text{PEEP} + \text{autoPEEP})}$$

Normal C_{dyn} value is 100 mL/cmH_2O/L.

Alveolar Gas Equation

$P_AO_2 = (P_{ATM} - P_{H_2O})F_iO_2 - PCO_2/R_Q$

where

P_AO_2 = partial pressure of O_2 in the alveolus under present conditions
P_{ATM} = current, local atmospheric pressure
P_{H_2O} = vapor pressure of water at body temperature and 100% relative humidity
F_iO_2 = fraction of inspired O_2
PCO_2 = partial pressure of CO_2 in arterial blood
R_Q = respiratory quotient

At sea level,

$P_AO_2 = 150 - 1.25 \times PaCO_2$

Weaning Indices

Rapid Shallow Breathing Index (RSBI)

RSBI = f/V_T
where
f = frequency (breaths/min)
V_T = tidal volume (L)
Successful weaning is usually accomplished if the RSBI is less than 105 breaths/min/L

Compliance, Rate, Oxygenation, Pressure (CROP) Index

CROP index = $[C_{dyn} \times P_{imax} \times (PaO_2/P_AO_2)]$/rate
where
C_{dyn} = dynamic compliance
P_{imax} = maximal inspiratory pressure
Weaning success occur if value is more than or equal to 13 mL/breath/min.

by mansdocs.com

Appendix 3: Acid-Base Balance, Renal Formulae and Values

$pH = pKA + \log (HCO_3/CO_2)$
$[H^+]$ (nEq/L) = 24 × (PCO_2/HCO_3); using PCO_2 40 mm Hg, HCO_3 24 mEq/L, then $[H^+]$ = 40 nEq/L.

Primary disorder	*Expected result*
Metabolic acidosis	Expected $PCO_2 = (1.5 \times HCO_3) + (8.2)$
Metabolic alkalosis	Expected $PCO_2 = (0.7 \times HCO_3) + (21.2)$
Acute respiratory acidosis	$\Delta pH = 0.008 \times \Delta PaCO_2$ Expected $pH = 7.40 – [0.008 \times (PaCO_2 – 40)]$
Acute respiratory alkalosis	$\Delta pH = 0.008 \times \Delta PaCO_2$ Expected $pH = 7.40 + [0.008 \times (PaCO_2 – 40)]$
Chronic respiratory acidosis	$\Delta pH = 0.003 \times \Delta PaCO_2$ Expected $pH = 7.40 – [0.003 \times (PaCO_2 – 40)]$
Chronic respiratory alkalosis	$\Delta pH = 0.003 \times \Delta PaCO_2$ Expected $pH = 7.40 + [0.003 \times (PaCO_2 – 40)]$

Base Deficit

HCO_3 deficit = (desired HCO_3 – observed HCO_3) × 0.4 × [body weight (kg)]

Renal Equations

Glomerular filtration rate (GFR)
Below 45 years: GFR = 12.49–0.37 (age)
At or above 45 years: GFR = 153–1.07 (age)

Cockcroft and Gault

Creatinine clearance (mL/min)

$$= \frac{\text{Body weight (kg)}}{\text{Serum creatinine (mg/dl)}} \times \frac{140 \times \text{age}}{72}$$

In women, the value obtained from this equation is multiplied by a factor of 0.85.

Indices in Acute Renal Failure

Index	*Prerenal*	*Acute tubular necrosis*
Specific gravity	> 1.020	< 1.010
Urinary osmolality (mOsm/kg H_2O)	> 500	< 350
U_{osm}/P_{osm}	> 1.3	< 1.1
Urinary Na^+ (mEq/L)	< 20	> 40
U/P Cr	> 40	< 20
RFI	< 1	> 1
FENa (%)	< 1	> 1

(Cr: Creatinine, P: Plasma, RFI: Renal failure index, U: Urine, and F_ENa: Fractional excretion of sodium)

Serum osmolality:
Osm = $2Na^+$+BUN (mg/dL)/2.8 + glucose (mg/dL)/18

Urine Analysis in Different Conditions

Condition	*Findings*
Prerenal failure	SG: > 1.015
	pH: < 6
	Prot: trace to 1+
	Sed: sparse hyaline, fine granular cases or bland
Postrenal failure	SG: 1.010
	pH: > 6

Contd...

by mansdocs.com

Contd...

Condition	Findings
Acute tubular necrosis (ATN)	Prot: trace to 1+ Hb: + Sed: RBCs, WBCs "Muddy" brown urine SG: 1.010 pH: 6–7
Glomerular diseases	Prot: trace to 1+ Blood: + Sed: RBCs, WBCs, RTE cells, RTE casts, pigmented casts SG: > 1.020 pH: > 6 Prot: 1 to 4+
Vascular diseases	Sed: RBCs, RBC casts, WBC, oval fat bodies, free fat droplet, fatty casts SG: > 1.020 if proglomerular pH: > 6 Prot: trace to 2+
Interstitial diseases	Sed: RBCs, RBC casts with glomerular involvement SG: 1.010 pH: –7 Prot: trace to 1+ Sed: WBCs, WBC casts, eosinophils, RBCs, RTE cells

(RBCs: Red blood cells, RTE: Renal tubular epithelial cells, WBCs: White blood cells, SG: Urine-specific gravity, Prot: Protein, and Sed: Urinary sediment)

by mansdocs.com

Appendix 4: Scoring System Used in ICU

Table 1: The Sequential Organ Failure Assessment (SOFA) Score*

			SOFA score		
Variables	*0*	*1*	*2*	*3*	*4*
Respiratory Pao_2/FiO_2, mm Hg	> 400	≤ 400	≤ 300	≤ 200†	≤ 100†
Coagulation Platelets × $10^3/\mu L$‡	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL‡	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Cardiovascular Hypotension	No hpotension	Mean arterial pressure < 70 mm Hg	Dop ≤ 5 or dob (any dose)§	Dop > 5, epi ≤ 0.1, or norepi ≤ 0.1§	Dop > 15, epi > 0.1, or norepi > 0.1§
Central nervous system Glasgow Coma Score Scale	15	13–14	10–12	6–9	< 6
Renal Creatinine, mg/dL or urine output. mL/d#	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9 or < 500	> 5.0 or < 200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop; dopamine, Epi; epinephrine; and FiO_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in µg/kg 1 minute).
#To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

Simplified Acute Physiology Score II (SAPS II)

Parameter			*Value (score)*				
HR			< 40 (11)	40–69 (2)	70–119 (0)	120–159 (4)	> 160 (7)
SBP			< 70 (13)	70–99 (5)	100–199 (0)	> 200 (2)	
Temperature					< 39°C (0)	> 39°C (3)	
PaO_2/FiO_2	< 100 (11)	100–199 (9)	> 200 (6)				
UO (mL)		< 500 (11)	> 500 (4)		> 1000 (0)		
Serum urea					< 28 (0)	28–83 (6)	> 84 (10)
TLC(10^3/cc)				< 1(12)	1–20 (0)	> 20 (3)	
K*				< 3 (3)	3–4.9 (0)	> 5 (3)	
Na*				< 125 (5)	125–144 (0)	> 145 (1)	
Bicarb			< 15 (6)	15–19 (3)	> 20 (0)		
Bilirubin					< 4 (0)	4–5.9 (4)	> 6 (9)
GCS	< 6 (26)	6–8 (13)	9–10 (7)	11–13 (5)	14–15 (0)		

Age	score
<40	0
40–59	7
60–69	12
70–74	15
75–79	16
>80	18

Chronic disease:
Metastatic cancer–9
Hemat. malig–10
AIDS–17

Type of admission:
Sched. surgical–0
Medical–6
Emer. surgical–8

(HR: Heart rate; SBP: Systolic blood pressure; TLC: Total lung capacity; GCS: Glasgow coma score; AIDS: Acquired immunodeficiency syndrome).
Source: Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270(24):2957-63.

by mansdocs.com

Multiple organ dysfunction score (MODS)

	0	*1*	*2*	*3*	*4*
Respiratory PO_2/FiO_2	> 300	226–300	151–225	76–150	< 75
Renal S creatinine (μmol/L)	< 100	101–200	201–350	351–500	> 500
Hepatic Serum bilirubin (μmol/L)	< 20	21–60	61–120	121–240	> 240
Cardiovascular (PAR)	< 10	10.1–15	15.1–20	20.1–30	> 30
Hematological platelet count (100/μL)	> 120	120–80	80–50	50–20	< 20
Neurological (GCS)	15	14–13	12–10	9–7	< 7

(GCS: Glasgow coma scale; PAR: Pressure-adjusted heart rate).

Logistic Organ Dysfunction System (LODS)

System	*Parameter*	*Value (Score)*				
Neurological	GCS	14,15 (0)	13–9 (1)	8–6 (3)	5–3 (5)	
CVS	HR	> 140 (1)	140–30 (0)	< 30 (5)		
	SBP	> 270 (3)	240–269 (1)	70–89 (1)	69–40 (3)	< 40 (5)
Hematological system	TLC (1,000/cc)	< 1 (3)	1–2.4 (1)	2.4–50 (0)	> 50 (1)	
	Platelet (10^3/cc)	< 50 (1)	> 50 (0)			
Respiratory system	PaO_2	< 150 (3)	> 150 (1)			
Hepatic system	Bilirubin (mg/dL)	< 2 (0)	> 2 (1)			
	PT	N+3 (0)	> N+3 (1)			
Renal system	Urea (mg/dL)	> 120 (5)	119–60 (3)	59–35 (1)	< 35 (0)	
	Creatinine (mg/dL)	> 1.16 (3)	1.59–1.2 (1)	< 1.2 (0)		
	UO (L/24 hour)	> 10 (3)	10–0.75 (0)	0.75–0.5(3)	< 0.5 (5)	

(HR, Heart rate; SBP: Systolic blood pressure; TLC: Total lung capacity; GCS: Glasgow coma score; AIDS: Acquired immunodeficiency syndrome; CVS: Cardiovascular system).

Mortality Probability Model (MPM)

Variable	*1*	*0*	β
Level of consciousness	Coma/deep stupor	No coma/deep stupor	2.89
Admission	Emergency	Elective	1.2671
Prior CPR	Yes	No	1.0137
Cancer	Present	Absent	0.94131
CRF	Present	Absent	0.64049
Infection	Probable	Not probable	0.047789
Previous ICU admission in previous 6 months	Yes	No	0.43946
Surgery before ICU admission	Yes	No	–0.37987
SBP			–0.04591
HR	10 beat/min relative risk		0.00736
Age	10 years relative risk		0.047789
Constant			–2.9678

(ICU: Intensive care unit; CRF: Corticotropin-releasing factor; HR: Heart rate; SBP: Systolic blood pressure).

by mansdocs.com

Cellular Injury Score (CIS)

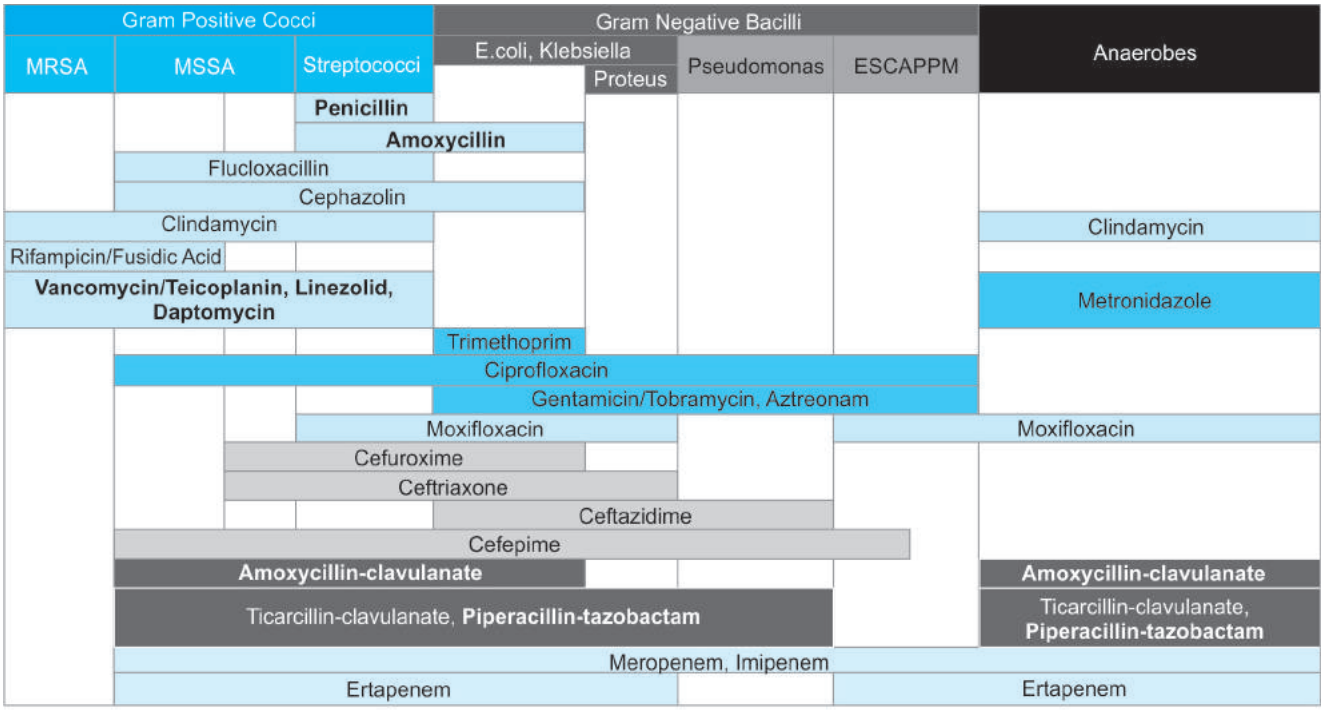
	0	*1*	*2*	*3*
AKBR	> 0.71	0.7–0.41	0.4–0.26	<0.25
OG mOsm/kg	< 2.2	2.3–10	10.1–20	>20.1
Blood Lactate mg/dL	< 16	17–25	25–50	>51

CIS score 0–1:	6.7% mortality rate
2–3:	40%
4–5:	70%
6–7:	82%
8–9:	100%

(AKBR: Arterial ketone body ratio; OG: Osmolality gap).

by mansdocs.com

Appendix 5: Spectrum of Commonly Used Antibiotic in ICU



Antibiotics in bold also cover Enterococcus Faecalis, For simplicity, atypical organisms are not included above.
ESBL-producing organisms are not susceptible to most antibiotics containing a beta-lactam ring; Carbapenems are the usual agent of choice.
This antibiotic spectra chart is intended as a rough guide pending specific identification and sensitivities- it does not replace expert ID advice.

(MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*).

by mansdocs.com

Index

Page numbers followed by *f* refer to figure, *fc* refer to flowchart, *b* refer to box and *t* refer to table.

A

Abdominal compartment syndrome (ACS) 325, 516
  timing designations of 517*t*
Abdominal examination 119
Abdominal perfusion pressure (APP) 516, 519
Abdominal problems 326
Acetaminophen 531
Acetaminophen hepatotoxicity 206
Acetyl-para-amino-phenol (APAP) 531
Acid-base balance 631
  analysis of 276
  disorders of 276
Acid-base disorders 277, 277*t*
  in critical care 276
Acid-base disturbances 306
Acid-base nomogram 278*f*
Acid-base status 359
Acidosis 394
  and hyperglycemia in diabetes ketoacidosis, management of 496*fc*
  diagnosis 282
  normal anion gap 280*t*
Acute physiology score II 633*t*
Adenosine 135
  triphosphate (ATP) 205, 308, 387, 387
Adequate mentation 594
Adequate oxygenation 594
Adequate pulmonary function 594
ADHF, treatment of 121
Adjuncts to primary survey and resuscitation 321
Adrenal insufficiency 514
Adult ECMO 616
Adult liver transplantation 253
Adult respiratory distress syndrome (ARDS) 323, 560*f*
Adverse events and mortality 612
Aero probe 624
  catheter 624*f*
Aerochamber 622*f*
Aeroneb vibrating mesh nebulizer 623*f*
Aerosol delivery 621
  systems 622*f*, 623
  in mechanical ventilation 621
Aerosol device vibrating plates 623
Aerosol therapy mechanical ventilation 621
AG metabolic acidosis, high 279
Aggressive diuresis 619
Air leaks, massive 608
Air trapping 584*f*
Airflow obstruction 602
Airway 302, 527
  anatomy of 9, 10*f*
  assessment of difficult 19
  breathing
    and circulation 413
    compression 66
  burns 489
  diameter, decrease in 571
  high mean 588
  management 552*t*
    difficult 19, 21*fc*
    in ICU 9
    invasive 17
    non-invasive 11
    techniques 9, 10
  obstruction 14, 413, 506
  pressure 570*f*
    continuous positive 334, 579*f*, 587, 596
  release ventilation (APRV) 587, 587*f*
  resistance and alveolar pressures, relation between 572*f*
  resistance changes 584*f*
  resistance, disadvantages of increased 571
  with cervical spine control 315, 486
AKI, nonoliguric 263
Alanine aminotransferase (ALT) 205, 253
Alanine transaminase 208
Albuminuria 527
Alcohol 526
  dehydrogenase (ADH) 540
  poisoning 539
Aldosterone antagonists 124
ALF, causes of 207
Allopurinol 500
Aluminum and zinc phosphide 533
Amino acids 523
Aminoglycosides 424
Amphetamine 526, 532
Amyotrophic lateral sclerosis (ALS) 598
Anaerobic threshold (AT) 237
Analgesia 487
  and sedation 325
  postoperative 352
Analgesics 385
Anemia 54, 125, 344, 459, 526
  of infancy 361
Anesthesia 34
  considerations, postoperative 346
  for liver transplantation 233
  general endotracheal (GETA) 372, 374
  maintenance of 244
Anesthetic induction 244
Anesthetic management of
  brain-dead donors 235
  donor 234
  living donors 234
  recipients 235
Angiotensin converting enzyme (ACE) 148, 274
  inhibitors 115, 123
Angiotensin receptor blocker (ARB) 124, 274
Anicteric leptospirosis 468
Anidulafungin 435
Anion gap 276, 278
  causes of high 280*t*
Anomalies of pancreas 216
Anoxic injury 512
Anteroposterior (AP) 560
Antiallergics 385
Antiarrhythmic drugs 139*t*, 510
Antibiotic prophylaxis 222
Antibiotic resistance 194
Antibiotic therapy 187
  duration of 188, 446
  for CAP 187
Antibiotic, selection of 193
Antibiotic, use of 191
Anticholinergic 526
Anticoagulation 114, 618
  strategies 132
Antidiuretic hormone (ADH) 296
Antidiuretic receptor antagonist 303
Antidotes 529
  list of 530

by mansdocs.com

Antiepileptic drugs 449
Antihistamines 526
Antihyperuricemic therapy 500
Anti-inflammatory and immunotherapy 395
Antimalarial therapy 459
Antimicrobial therapy 428, 429, 430
Antiphospholipid antibody 373
Antiplatelets 114
Anti-snake venom (ASV) 545
Antitumor therapy for disease control 502
Aortic dissection 150
Aortic Doppler 31
Aortic flow augmentation, continuous 127
Apnea 19
ARDS
  disorders associated with 196
  extrapulmonary 196
  management algorithm 200
Arrhythmias 44
Arrhythmogenic right ventricular cardiomyopathy (ARVC) 118
Artemether 459
Arterial blood gases (ABG) 5, 230, 276, 318, 374, 552, 590
  analysis 230
Arterial blood pH
  high 284
  low 277
Arterial blood pressure
  direct (ABP) 26
  monitoring invasive 26
Arterial carbon dioxide, pressure of 407
Arterial oxygen saturation 552*f*
Arterial pulse pressure 43*f*
Arterial volume, decreased effective 228
Arterial waveform 27*f*
Arteriovenous (AV) 230
  malformations (AVMS) 374
  oxygen content difference 628
Artery, umbilical 361
  catheter 559
Aspartate aminotransferase 205, 208, 217, 253
Aspartate transaminase (AST) 78
Aspergillosis, pathogenesis of 436
Aspergillus infections 439
Aspiration 191
  pneumonitis 561*f*
Assist controlled mechanical ventilation 574
Asthma 364, 571
ASV, indications of 545*t*
Asymptomatic patient 303
Asystolic arrest 155
Atlanta and recent revision, comparison of 218*t*
Atrial fibrillation 130, 131*f*, 133*t*
  in heart failure patients, management of 124
  follow-up investigation of rhythm management 131
Atrial flutter 132, 133*f*
Atrial hypertension, left 195
Atrial pressure
  left 627
  right 24, 174, 627
Atrial tachycardia 134, 135*f*
Atrioventricular blocks 141, 143*f*, 155
Atrioventricular nodal re-entrant tachycardia 134, 134*f*
Atrioventricular node dysfunction 141*t*
Atropine 143
Audit cycle 99*f*
Autoimmune hepatitis 370
Autopeep 584*f*
AVPU score 6

B

Baby lung 197
  concept 197
Bacterial peritonitis, spontaneous (SBP) 226, 431
Bacteriuria 452
Bag and mask ventilation 14*f*
Balance of coagulation 239*f*
Balloon atrioseptostomy 177
Banff score 254
Barbiturates 402, 526
Barotrauma 197
  existing 612
  predisposition to 612
Base deficit 631
Benzodiazepine infusion 402
Benzodiazepines 526
Bilateral intercostal drain tube with massive subcutaneous emphysema 557*f*
Bi-level mode 589, 589*f*
  with pressure support 589*f*
Bi-level positive airway pressure (BIPAP) 587, 596, 597
Bi-level with pressure support 589*f*
Biliary complications 260
Biliary pancreatitis
  mild 223
  severe 223
Biopsy 192
Bipyridyl compound 538
Bisphosphonates 308
Blantyre coma score (BCS) 459
Blast injury 486
Bleeding time 544
Blind bronchial suction (BBS) 192
Blind bronchoalveolar lavage (BAL) 192
Blood chemistry 185
Blood flow velocity (FV) 341
Blood gas analysis 527
Blood pressure (BP) 145, 383, 407, 554, 627
  invasive 241
  low 25
  non-invasive (NIBP) 241
  targets in case of hypertension 77
Blood products 244
Blood sugar 527
Blood transfusions 366
Blood urea nitrogen (BUN) 119, 217, 301
Bloodstream infection (BSI) 434
Body mass index (BMI) 517, 550
Body positioning 191
Body surface area (BSA) 485, 627
  total (TBSA) 484
Body water, total 296
Body weight, total 552
Bohr effect, double 360
Bone marrow failure 526
Bosentan/ambrisentan 177
Bowel loops 564*f*
Bradyarrhythmias and conduction block 140
Bradycardias 155
Brain 208
  dead donors, physiological derangements in 235*t*
  death 75
    and organ donation 327
  herniation syndrome, signs of 409
  natriuretic peptide (BNP) 172, 396
  swelling, postoperative 348
Brainstem death (BSD) 76
  tests of 75
Breast 449
Breath 573
  positive pressure 570*f*
Breathing 5, 302, 486
  and ventilation 317
  circulation 527
  mechanical restriction of 486
  problems 316
  response to 230
  spontaneous 42, 570*f*, 577*f*, 587*f*, 588
  trial, spontaneous 592, 593, 594
    failure criteria of spontaneous 594
  work of 573, 574, 589, 593, 602
British thoracic society criteria 186
Bronchoalveolar lavage (BAL) 196, 437
Bronchopleural fistulas 607, 608
Bronchopneumonia 184
Bronchoscopic sampling 192

by mansdocs.com

Bronchoscopy 185
Bronchospasm 535
Brugada criteria ventricular tachycardia 138
Brush, protected specimen (PSB) 192
Budd-Chiari syndrome 370
Bundle branch block
left 111, 127
right (RBBB) 157
Bungarus caeruleus 545
Burn area, assessment of 487
Burn
contact 485
flame 485
flash 485
inhalation and electrical injury 483
major 485
types of 485

C

Calcineurin inhibitors 257, 274
Calcitonin 502
Calcium and magnesium, disorders of 306
Calcium channel blockers (CCBs) 124
Calcium homeostasis 306
Calcium metabolism 306
disorders of 307
Calcium, functions of 306
California intensive care outcomes (CALICO) 82
Candida albicans 211, 435
germ tube 437
Candida glabrata 435
Candida krusei 435
Candida parapsilosis 435
Candida tropicalis 435
Candiduria 452
CAP, pathogenesis of 184
Capillary refill time (CRT) 25, 383, 390
Carbamate 534
Carbamate poisoning 536
Carbapenems 423
Carbon dioxide 413
Carbon monoxide 486
poisoning 486, 534
Carboxyhemoglobin 486, 534
Cardiac arrest 64
Cardiac arrhythmias 129
Cardiac conduction system 140*f*
Cardiac dysfunction 347
Cardiac effects 293
Cardiac index (CI) 242, 627
Cardiac life support, advanced 65, 67, 510
Cardiac magnetic resonance imaging 172
Cardiac output (CO) 169, 627
continuous (CCO) 30
monitoring 241
minimally invasive 30
Cardiac resynchronization therapy 127
Cardiocerebral resuscitation (CCR) 66
Cardiogenic pulmonary edema (CPE) 196
Cardiogenic shock 34
Cardiopulmonary
complications 343
exercise testing (CPET) 237
resuscitation 64, 383, 479
system 235
Cardiovascular
complications 335
dysfunction 334
examination 119
management 334
manifestations 307
stability 274
support 377, 392
system 255, 351, 510
Cardioversion of atrial fibrillation 133*t*
Cardioverter defibrillator, automated implantable 556*f*, 559
Carotid sinus massage 135
Carvedilol prospective randomized cumulative survival 123
Caspofungin 441
Catecholamine refractory shock 396
Catheter embolectomy 167
Catheter-related bloodstream infection (CRBSI) 430, 435
Causative agents 184
CBF and $PaCO_2$ and PaO_2, relationship between 606*f*
CECT criteria 218
Cefotaxime 423, 425
Cefoxitin 423
Ceftazidime 423, 425
Ceftriaxone 423
Cell death 33
Cell lung
carcinoma, small (SCLC) 503
carcinomas 503
Cellular injury score (CIS) 635*t*
Central nervous involvement 463
Central nervous system (CNS) 75, 240, 257, 276, 308, 346, 395, 407, 440, 449, 452, 470, 502, 532
Central neuraxial blocks (CNBs) 372
Central pontine myelinolysis 303
Central tendon of diaphragm 564
Central venous
catheter (CVC) 434, 437
line 556
pressure (CVP) 27*f*, 41, 76, 122, 221, 234, 242, 273, 323, 374, 391, 495, 517, 628
Cerebral blood flow (CBF) 70, 321, 341, 351, 406, 605
and intracranial pressure, relationship between 605*f*
monitoring 351
Cerebral blood volume (CBV) 407
Cerebral edema 349*f*
Cerebral failure 490
Cerebral ischemia, delayed 339-341
Cerebral malaria 459
Cerebral metabolism 70
Cerebral oxygenation and metabolism 352
Cerebral perfusion pressure (CPP) 209, 351, 406, 407, 417, 518, 605
Cerebral protection 395
Cerebral salt wasting (CSW) 305, 344
syndrome 304
Cerebral sysmptoms in hyponatremia 302
Cerebrospinal fluid (CSF) 278, 321, 338, 395, 406, 440, 452, 468
Cerebrovascular accident (CVA) 150, 448
Cervical spine
clearance of 331
immobilization 11
injury (CSI) 316
Cesar trial 619
Charcoal, multidose activated 529
Chest automated implantable cardioverter defibrillator 559*f*
Chest imaging 195
Chest in lying posture 560*f*
Chest in neonate with low-lying distal end 558*f*
Chest pain of MI, classical 111
Chest pneumothorax on right side with malpositioned intercostal drain tube 557*f*
Chest radiography 120
Chest trauma 606
Chest with tracheostomy 557*f*
Chest X-ray 114, 185, 196, 230, 365, 547
Children versus adults 546
Child-turcotte pugh (CTP) 226, 227*t*, 233
Chin-lift maneuver 315, 315*f*
Cholecystectomy 223
Ciaglia's technique 19
Circulatory control 323
Circulatory devices, mechanical 125
Cirrhotic patients with life-threatening infections 431
Cirrhotics, classification of 226
Clavulanic acid 425
Clevidipine 148
Clostridium difficile 258, 449
Clotting time (CT) 544
activated (ACT) 618, 619

by mansdocs.com

CMV and HFOV, comparison of 615*f*
CNS
causes 593
disorders 373
trauma 14
Coagulation monitoring 243
Coagulation, zone of 484
Coagulopathy 208
management of 210
Cobra snake 543
Cocaine 526, 532
Cockcroft and gault 631
Codeine 538
Coenzyme A (CoA) 540
Cold air-forced cooling 72
Cold shock 387
Collapse of lung
left 556*f*
right with mediastinal 557*f*
Colloid solutions 39
Colonization index (CI) 436
Colonization, control of 191
Coma 539
cocktail 527
Combined spinal-epidural anesthesia (CSEA) 373
Combitube 17*f*
Community acquired pneumonia (CAP) 183, 184*t*
severe 187
Community-acquired bacterial meningitis 431
Community-acquired pneumonia 428, 430, 431
right sided 183*f*
with ARF 597
Compensatory anti-inflammatory response syndrome (CARS) 58, 388
Compliance changes 585*f*
Confidence interval (CI) 554
Congestive cardiac failure 560*f*
Congestive heart failure (CHF) 117, 279, 303
Consciousness 382
level of 319
Consequences of cardiopulmonary resuscitation 514
Convection, principle of 269*f*
Conventional coagulation tests 243
Conventional mechanical ventilation (CMV) 588, 608, 614
Cooling, external 71
Cooling, extracorporeal 72
COPD patients 598
Coral snake 543
Cormack-Lehane classification 19
Coronary artery
disease (CAD) 235
perfusion pressure 627
right (RCA) 171
Coronary intervention, post-percutaneous (PCI) 111
Coronary syndrome, acute (ACS) 111, 146
Corticosteroids therapy 395
C-reactive protein (CRP) 333, 390
Creatine kinase 114
Creatine phosphokinase (CPK) 462, 468
Cricothyroidotomy 18
Critical care unit 88
Critical chain method, active (ACCM) 391
Critical tropical infections, management of 466*fc*
Crystal-dependent mechanism, classical 499
Crystalloid solutions 39
Curling of distal end of central venous line 558*f*
Cyanide poisoning 487
Cyanotic breath holding spells 399
Cycle variable 573
Cytomegalovirus (CMV) 216, 274, 446, 454
infection 454

D

Daboia russelii 545
Decelerating-ramp flow 583*f*
Decontamination 536
Deep vein thrombosis (DVT) 160, 344, 348, 365, 565, 518
Dengue 461, 469
fever, severe 460
Dense spongy appearance 231*f*
Depolarizations, spreading 339
Detergent poisoning 541
Dextrose 523
Diabetes insipidus 77, 378
Diabetes ketoacidosis (DKA) 494
Diabetes mellitus (DM) 427
Diabetic ketoacidosis (DKA) 277, 494
Dialysis quality initiative, acute (ADQI) 267
Dialysis, slow low efficiency daily 271
Diarrhea 535
Diastolic blood pressure (DBP) 627
Dichlorodiphenyltrichloroethane (DDT) 537
Diffusion, process of 269*f*
Digital subtraction angiography (DSA) 338
Dilated cardiomyopathy (DCM) 118
Disability 320, 383
problems 316
Discrete arteriovenous fistula 231*f*
Disease control and prevention (CDC) 425
Disseminated intravascular coagulation (DIC) 196, 365, 373, 388, 456, 476
Distal airway, secretions in 192
Diuretic therapy 303
Dobutamine 122
stress echocardiogram (DSE) 256
Donor liver, suitability of 78
Donor management, principles of 76, 236*t*
Dopamine 122, 413
Double-lumen endotracheal tube 608*f*
Drug delivery 625*f*
by jet nebulizer in ventilated patients 625
by MDI in ventilated patients, technique for 625
Drug fevers 449
Drug screening 527
Drug therapy 363
Drug, assessment of disability 6
Drug-induced
bradycardias 155
injury 204
Drugs, newer unproven 223
Dynamic hyperinflation 602
Dysnatremia 344

E

Early-extubation (fast-tracking) 246
ECG monitoring 321
Echinocandins 440
Echis carinatus 545
ECHO 547
Echocardiography 30, 31, 120, 172
ECMO
adjustments during 618
starting 618
steps in starting 618
types of 616
Edema, origin of 196
Education, quality of 105
Ejection fraction (EF) 117
Elastance 571
Electrical activation of diaphragm 575
Electrical injury 485
Electrocardiogram 111, 112, 120, 129, 502
Electrocardiography (ECG) 14
Electroencephalogram monitoring 352
Electroencephalograph (EEG) 415, 511
Electrolytes 523, 527
Embolectomy 166
surgical 167

by mansdocs.com

Embolotherapy 231
Emergency department 154
Emergency management 332
Emergency room 314
Emergency transcutaneous pacing 159
Emesis 535
Emphysema 571
Empiric anticoagulation 163
Empirical therapy 438
Enalaprilat 148
Encephalitis 415
Encephalopathy, grade III/IV 208
End-expiratory occlusion test 30
Endocrine 449
  problem 258
End-of-life care (EOLC) 478
End-of-life discussions (EOLD) 478
Endoscopic ultrasonography 220
Endoscopy 527
Endothelin receptor antagonists 177
Endotoxin-macrophage hypothesis 59
Endotracheal 603
  and nasogastric tubes 556*f*, 558*f*
  intubation 9, 17, 555
  intubation with cervical spinal injury 333
  mechanical ventilation (ETMV) 595
  tube (ET) 317, 415, 558*f*, 622
    low-lying 556*f*
Environmental control, exposure and 321
Enzyme-linked immunesorbant assay (ELISA) 461, 467, 544
Epilepticus, complications of status 399*t*
Epstein-Barr virus (EBV) 216
ERCP in acute pancreatitis 223
ESBL classification 421
Escharotomy 488
Esmolol 149, 414
Ethanol poisoning 540
Ethical considerations and end-of-life care 178
Ethics committee, role of 476
Ethylene glycol 281
European antibiotic resistance surveillance system (EARSS) 422
European Heart Association (EHA) 114
Exacerbation of COPD, acute 428, 597
Expiratory pressure, presence of positive end (PEEP) 596
Extended-spectrum beta-lactamase (ESBL) 193
External defibrillator, automated (AED) 64
Extracellular fluid (ECF) 38, 38*t*
  volume (ECF) 284
Extracellular volume (ECV) 299
Extubation 592
Exudative phase 196

F

Falciparum malaria, severe 457, 458*t*
Fasciotomy 488, 489
Fat free mass (FFM) 553
Fatal envenomations 543
Fatty liver of pregnancy, acute (AFLP) 204, 370
Febrile encephalopathy 466
Febrile neutropenia 443
Febrile neutropenia, management of 444, 445*f*
Feeding 191
Fentanyl 538
Fetal circulation 361
Fetal hemoglobin 360
Fetal monitoring in pregnancy 376
Fetal oxygenation 359*t*, 362*f*
Fever 344
  beneficial effects of 448
  noninfectious causes of 449
  tropical 465
  with acute respiratory distress syndrome (ARDS) 465
  with central nervous system involvement 457
  with hepatorenal dysfunction 457
  with multiorgan dysfunction 466
  with pulmonary dysfunction 456
  with shock 457
  with thrombocytopenia 456
Fibrinolytic agents and doses 165*t*
First-degree atrioventricular block 141, 142*f*
Flexometallic laryngeal mask airway 16*f*
Flow asynchrony 585*f*
Flow cycled 573
Flow limit 573
Flow trigger 573, 576, 600*f*
Flow-time waveforms 581
Fluconazole 435, 440
Fluid and electrolytes 256
Fluid and electrolyte disturbances 460
Fluid challenge 28, 41*t*
Fluid challenge, critical components of 42*t*
Fluid in peritoneal cavity 565*f*
Fluid management 619
  in diabetes ketoacidosis 495*fc*
  postoperative 352
Fluid replacement, type of 300
Fluid resuscitation 221, 320*t*, 391, 487
  in compensated shock 463*fc*
  in decompensated shock 462*fc*
Fluids and blood products 247
Fluorescent antibody assay, indirect (IFA) 467
Fluoroquinolones 424
Food and drug administration (FDA) 165, 241
Forced expiratory volume 332, 365
Foreign body obstruction 385
Foreign exchange program 105
Fosfomycin 424
Free fatty acids 547, 553
Fresh frozen plasma 234
Fungal DNA, detection of 437
Fungal infections 428
  invasive 434
Furosemide 308

G

Gas delivery 573
Gas exchange 360
Gastric catheter 321
Gastric tonometry 34
Gastrointestinal
  support 395
  system 227, 257, 514, 529, 533
  tract (GIT) 281, 308, 449
Glasgow coma scale 351*t*, 316, 338, 352, 383, 384*t*, 408, 459
  scoring 321*t*
Glomerular filtration rate (GFR) 122, 226, 263, 267, 518, 552, 588, 631
Glycemic control 344
Grading hypercalcemia of malignancy 502
Graduated compression stockings (GCS) 335
Graft failure, primary 259
Graft function 274
Granulocyte colony stimulating factor 432, 455
Grigg's technique 19
Gut hypothesis 58
Gut-associated lymphoid tissue (GALT) 522

H

Haemophilus influenza 428
Haemorrhage
  class I 319
  class II 319
  class III 319
  class IV 320
  subarachnoid 337, 351
Harmless acute pancreatitis score (HAPS) 217
Harris-Benedict equation (HBE) 521, 553
Health evaluation
  acute 60, 79, 434
  chronic 60, 79, 434

by mansdocs.com

Healthcare-associated pneumonia 190
Heart block, complete 143
Heart failure 117, 427, 490
ACC/AHA stage of 118
acute 152
decompensated (ADHF) 117
chronic (CHF) 121
functional classification of 118
management of right 169
national registry, acute decompensated 119
pathophysiology of 118
treatment for right 179
Heart rate (HR) 23, 387, 594
Heat and moisture exchange (HME) 334, 625
HELLP syndrome 370
Hematological/coagulation system 239
Hematology 553
Hematuria 527
Hemodialysis 459, 490, 529
role of 501
Hemodynamic changes in right ventricular failure 169
Hemodynamic formulae and values 627
Hemodynamic monitoring 24
in ICU 23
Hemodynamic parameters 175*t*, 627
Hemodynamic stability 273
Hemodynamic support 162
Hemodynamically unstable patients 270
Hemodynamics, management of 210
Hemodynamics/renal failure 208
Hemoglobin 323, 359, 414, 486, 534, 527
Hemolysis 526
elevated liver enzymes and low platelets (HELLP) 373
Hemoperfusion 529
Hemorrhage control, circulation with 318
Hemorrhage grading scale, Hunt and Hess subarachnoid 338*t*
Hemorrhage hydrocephalus, post subarachnoid 343*f*
Hemostasis 323
Hepatic artery thrombosis (HAT) 254, 260
Hepatic encephalopathy, grades of 206t
Hepatitis B virus (HBV) 203, 204
Hepatopulmonary syndrome (HPS) 226, 229, 232, 238, 255
versus portopulmonary hypertension 230*t*
Hepatorenal syndrome 226, 227*f*, 257
types of 227
Herbicide 534
Hereditary pancreatitis 216
Herniation syndromes 409*t*
Heroin 526
Heterometrus bengalensis 546
HFOV, indications of 614
High dependency unit 92, 458
High frequency ventilation 367
High intracranial pressure waveforms 411*f*
Higher oxygen affinity 360
High-frequency oscillatory ventilation (HFOV) 199
Histidine rich protein (HRP) 469
Homeostasis in chronic liver disease 240*f*
Hormone 307
Hospital admission decisions in CAP 186
Hospital/ICU management 332
Hospital-acquired pneumonia (HAP) 190
Host defense 326
Host related 188
Human immunodeficiency virus (HIV) 452
Humidification 191
during NIV 599
Humidifiers versus non-humidifiers aerosol delivery 626
Hydralazine 148
Hydration 500
Hydrocephalus 342, 349
Hydrocortisone therapy, low dose 432
Hydrogen 395
Hydroxyethyl starches (HES) 39
Hyperbaric oxygen (HBO) 486
Hypercalcemia 216, 501
severe 502
Hypercapnia 413
Hyperchloremic metabolic acidosis 282*t*
Hypercoagulopathy 348
Hyperemia, zone of 484
Hyperkalemia 292, 293, 499
causes of 289, 292
treatment of 294*t*, 500
severe 293
Hyperleukocytosis 505
Hypernatremia 77, 296, 298
consequences of 297, 298*f*
in critically ill patients 296
pathophysiology of 296
with increased total body solute 299
with pure water loss 299
with water and solute loss 298
Hyperosmolar 301
therapy 415
Hyperparasitemia 460
Hyperphosphatemia 499, 501
Hypertension
accelerated 145
acute postoperative 152
implications of intra-abdominal 518*f*
pathophysiology of intra-abdominal 517
Hypertensive emergency 145, 146
treatment of 147
Hypertensive urgency 146
Hypertonic crystalloids 39
Hypertonic saline 294, 415
Hypertriglyceridemia 216
Hypertrophic cardiomyopathy 118
Hyperventilation 208, 416
Hyperviscosity syndrome 505
Hypocalcemia 307, 394, 499
chronic 307
in ICU, causes of 307
Hypoglycemia 460
Hypokalemia 289, 290, 291, 291*f*
severe 292
treatment of 291
Hypomagnesemia 308
treatment of 309*t*
Hyponatremia 301
on brain 302
with severe symptoms 302
without severe symptoms, treatment of 303
Hypo-osmolar 301
hyponatremia, causes of 302*t*
Hypoparathyroidism 307
Hypothermia after cardiac arrest 70
Hypotonic crystalloids 39
Hypoxemia 230
Hypoxia 413
Hypoxic pulmonary vasoconstriction (HPV) 171, 173
and target arrhythmias 173
Hysteresis 571

I

ICP monitoring
role of 209
techniques of 324*f*
Icteric leptospirosis 468
ICU, antibiotic in 636
ICU care, supportive 173
ICU, clinical audit in 98
ICU management 208
of ALF 208
ICU patients, strategy for 521
ICU planning 88
ICU referrals, indications for 549
ICU setting, pacing in 154
ICU, audit and handoff in 98
ICU, management of specific infections in 457
ICU, scoring systems in 79
Ideal body weight (IBW) 552
ILV, use of 607

by mansdocs.com

Immune response in severe sepsis 388*f*
Immunofluorescence assay (IFA) 464
Immunosuppressants 274
Immunosuppressive therapy 259
Implantable cardioverter-defibrillator 127
Indian diploma in critical care
  medicine (IDCCM) 106
  nursing (IDCCN) 106
Indian Nursing Council (INC) 105
Indian Society of Critical Care Medicine (ISCCM) 106
Indocyanine green (ICG) 35, 246
Induced hypothermia 416
Inertial impact 621
Infections in postoperative period 259*t*
Infections, tropical 456
Infectious causes of fever 449
Infectious Disease Society of America (IDSA) 423, 429, 448
Inferior vena cava (IVC) 31, 41, 44, 165, 245, 558
Inflection point
  lower 582, 584*f*
  upper 584*f*
Information communication distribution transaction (ICTD) 90
Infrared spectroscopy 35
Injury, chemical 485
Injury, mechanisms of 485
Injury, primary 329
Insect stinging
  signs of severe 549
  symptoms of severe 549
Insecticide poisoning 534
Inspiration, termination of 599
Inspiratory pause, volume control with 577*f*
Inspiratory reserve volume (IRV) 587
Insulin, availability of 289
Integrated hypothesis 59
Integrated temperature management system 513*f*
Intensive care
  management 489
  unit (ICU) 3, 9, 23, 41, 59, 79, 87, 98, 117, 129, 147, 169, 203, 221, 253, 267, 273, 276, 296, 306, 314, 357, 365, 372, 421, 434, 448, 454, 456, 476, 478, 489, 494, 498, 521, 555, 580, 596, 602, 621
Intercostal drain tube 556
Interhemispheric subarachnoid haemorrhage, anterior 341*f*
Intermittent hemodialysis 270
Intermittent positive pressure ventilation (IPPV) 334, 569
Internal jugular
  pressure (IJP) 518
  vein (IJV) 374, 518
International normalized ratio (INR) 77, 517
Interstitial edematous pancreatitis 218
Interstitial lung disease (ILD) 598
Interstitial nephritis, acute (AIN) 265
Interventions, role of mechanical 177
Intestinal obstruction, acute 564*f*
Intra-abdominal hypertension IAH) 326, 516
  abdominal compartment syndrome, management of 519
Intra-abdominal pressure (IAP) 326, 516, 517*f*
  interpretation of 516*t*
  measurement of 519
Intra-aortic balloon pump counter-pulsation 125
Intracellular fluid 38*t*
Intracellular shifting 294
Intracranial hematoma, postoperative 349
Intracranial hemorrhage (ICH) 209, 410
Intracranial hypertension 324
  management of 209
Intracranial pressure 25, 71, 76, 241, 321, 339, 351, 373, 406, 407, 411, 470, 504, 510, 518
  causes of raised 408*b*
  increased (ICP) 400, 612, 614
  invasive 209
  management of raised 412
  monitoring 351, 409
    complications of 412
  waveforms 410, 411*f*
Intramuscular midazolam 401
Intraoperative management 241
Intrathoracic blood volume index (ITBVI) 242
Intravascular catheters, management of 451
Intravascular heat exchange
  catheter 72*f*
  device 72*f*
Intravenous access 391
Intravenous fluid 244, 532
  therapy 162
Intravenous heat exchange devices 72
Intravenous immunoglobulins 395
Intravenous levetiracetam 402
Intravenous valproate 402
Intrinsic positive end expiratory pressure 570
Introducer sheath 155
Intubating LMA 15, 17*f*
Invasive candidiasis, pathogenesis of 435
Iso-osmolar 301
Isopropyl alcohol 281
Isotonic crystalloids 39
Itraconazole 440
IVC filters 166

J

Japanese encephalitis (JE) 457
  virus 470
Jaw-thrust maneuver 315, 315*f*
Jet nebulizers 623

K

Ketamine 403
Ketoacidosis 279
Kidney disease
  acute versus chronic 263*t*
  chronic (CKD) 263, 273, 427
Kidney failure 490
Kidney injury, acute 263, 264*t*, 265*t*, 459
Kidney, dysfunction of 267*t*
Kidney, function of 267*t*
King cobra snake 543
Krait snake 543

L

Labetalol 149, 414
Lactate dehydrogenase (LDH) 205, 469
Lactic acidosis
  causes of 279
  management of 279
L-arginine 523
Laryngeal mask airway 14, 15*f*
  insertion of 16*f*
Lead placement, complications of 158
Lead time bias 85
Leakage 584*f*
Legionella 465
  pneumophila 183
Leptospira interrogans 461
Leptospirosis 461, 467
Leuckocyte count, total (TLC) 441
Leukocytosis 526
Leukopenia 526
Leukostasis 505
Levosimendan 123, 176
Lewis lead 136
  placement 137*f*
Lidocaine 403
Life support 64, 65
  extracorporeal 178
Life-sustaining therapies, forgoing of (FLST) 478

by mansdocs.com

Life-threatening hypocalcemia 501
Lipids 523
Liver allograft, function of 253
Liver disease
  chronic 228
  complicating pregnancy 369
  end-stage 253
  in pregnancy 369*t*
  vasopressin in chronic 229
Liver donor, live 234
Liver failure, acute 203, 205, 205*f*, 253
Liver support devices 212
Liver transplant patients 255
Liver transplantation 212, 229, 231
  three phases of 245
Living donor liver transplantation (LDLT) 235
LMA, flexible 15
Lobar pneumonia 184
Lobe consolidation, left upper 556*f*
Logistic organ dysfunction
  model 82
  system (LODS) 634*t*
Loop diuretics 308
Lower jaw, bimanual elevation of 11*f*
Low-molecular-weight heparin (LMWH) 164, 335
Lumbar puncture 452
Lumen tube, double 607*f*
Lund and Browder chart 488
Lung
  and respiratory failure 78
  assist, interventional 619
  capacity, total 552*t*, 590
  characteristics 570
  inflation of 570
  injury, acute (ALI) 195, 460, 597, 612, 613
    bilateral 608
  open 197
  overdistention of 584*f*
  preventing complete emptying of 603*f*
  transplantation 178
  ventilation, independent 607, 608
  water, extravascular 30
LV assist device 177
Lymphoblastic leukemia, acute (ALL) 505

M

Macroaggregated albumin (MAA) 238
  scanning 231
Magnesium metabolism 308
  disorders of 308
Malaria 469
  pathogenesis of severe 458*fc*
Malathion 534
Malignant hypertension 145
Malignant pericardial effusion 506
Mallampati classification 19
Mallampati score 20*f*
Mannitol 208
Marshall LI score 219*t*
MASCC scoring system 444*t*
Maternal and fetal oxygenation parameters 361*t*
Maternal fetal circulation 359, 359*f*
Maternal sepsis 373
Maximal inspiratory pressure (MIP) 592
Mean airway pressure 150, 208, 588, 627
Mean arterial blood pressure (MABP) 407
Mean arterial pressure (MAP) 23, 26, 76, 390, 411, 510
  intracranial pressure (MAP-ICP) 209
Mean pulmonary artery pressure (MPAP) 627
Mediastinal drain tube 556
Medical intensive care unit (MICU) 296
Medical therapy 231
Membrane antagonism 293
Membrane oxygenation
  circuit, extracorporeal 617*f*
  dynamics of extracorporeal 617*f*
  extracorporeal (ECMO) 178, 396, 616
Meningitis 415
Mental status 383
Mesangioproliferative glomerulonephritis 459
Meta-analysis of comparing enteral nutrition with parenteral nutrition 221*t*
Metabolic acidosis 277, 281
Metabolic alkalosis 285
  causes of 286*t*
  classification of 286*t*
  stepwise diagnosis 285, 287*t*
Metabolic and
  electrolytes 240
  respiratory alkalosis 289
Metabolic control 325
Metabolic derangements, correction of 394
Metabolic effects 293
Metabolic problem 258
Metabolic suppression therapy 416
Metastatic epidural spinal cord compression (MESCC) 504
Metered dose inhalers 621
Methadone 526
Methemoglobinemia 526
Methicillin-resistant staphylococcus aureus (MRSA) 428, 491
Methylenedioxymethamphetamine 532
Methylprednisolone 77
Micafungin 435, 441
Microcirculation, monitoring 34
Microcirculatory shunting 33
Microdialysis 352
Microscopic agglutination test (MAT) 462, 468
Middle cerebral artery (MCA) 408
Mild hypercalcemia 502
Mild pneumothorax on right side 558*f*
Mild-to-moderate potassium depletion 291
Milrinone 123, 176
Miosis 539
Moderate hypercalcemia 502
Molecular absorbents recirculation system (MARS) 212
Molecular-weight heparin, low (LMWH) 114
Monocytic leukemia, acute (AML) 505
Monro-Kellie doctrine 406
Moraxella catarrhalis 183, 428
Morison's pouch 565*f*
Morphine 121, 538
Mortality in acute
  liver failure 212*t*
  respiratory distress syndrome 195*t*
Mortality prediction model 81
Mortality probability model (MPM) 60, 634*t*
Mucosa-associated lymphoid tissue 522
Multidetector computed tomography-pulmonary angiography 165
Multi-organ dysfunction syndrome (MODS) 313, 470, 634*t*
Multi-pronged sepsis control strategy 392
Multivariate analysis 83
Musculoskeletal disorders 373
Musculoskeletal trauma 326
Myocardial infarction (MI) 111
  acute (AMI) 155
  classification of 111
  non-ST-segment elevation 115
Myocardial injury troponin 121
Myocardial ischemia 152

N

N-acetylcysteine 207, 532
N-acetyl-p-benzoquinone imine 531
Narcotics 526
Nasogastric tubes 555, 557*f*
Nasojejunal 221
Nasopharyngeal airway 12, 13*f*, 316

by mansdocs.com

National Health Policy (NHP) 104
National Nosocomial Infections Surveillance Systems (NNISS) 422
Nebulizer to breathing circuit, vibrating mesh 623*f*
Nebulizer, ultrasonic 623
Necrosis, infected 222
Needle cricothyroidotomy 317*f*
Neonatal ECMO 616
Nervous system control 324
Nesiritide 122
Neurocritical care 346
Neurogenic pulmonary edema 344, 347
Neurogenic stunned myocardium 343
Neurohormonal blockade 123
Neurological assessment 329
Neurological complications of SAH 340
Neurological monitoring 351
Neurological recovery 336
Neuromonitoring in SAH 339
Neuromuscular abnormalities 593
Neuromuscular causes 593
Neuromuscular effects 293
Neuromuscular manifestations 307
Neurophysiological tests 515
Neurosurgery, postoperative monitoring after 350*t*
Neurosurgical care, goals of postoperative 347
Neurosurgical complications
  management of postoperative 348
  prevention of postoperative 348
Neurosurgical ICU after operations 350*t*
Neurosurgical intensive care unit discharge criteria 352
Neurosurgical patients, management of postoperative 346
Neurotrauma patient, care of postoperative 325
Neutrally adjusted ventilatory assistance (NAVA) 601
Nicardipine 148
Nicotinamide adenine dinucleotide 540
Nitric oxide 57, 230, 523
  inhaled 176
Nitrofurantoin 424
Nitroglycerin 122, 149
Nitroprusside 122
NIV
  advantages of 596
  indications of 597
NIV in chronic conditions, indications of 597, 598
NIV settings 599
NIV success in COPD patients 600
NIV work 597
Nodal complete heart block (CHB) 143
Nonconvulsive SE (NCSE) 398
Noninvasive ventilation, applications of 595
Nonparacetamol-based drugs 205*f*
Nonsteroidal anti-inflammatory drug (NSAID) 209, 223, 227, 267
Non-stress tests (NSTs) 374
Norepinephrine 176, 413
Normovolemic intraoperative hemodilution, acute (ANIH) 234
Nosocomial pneumonia, treatment of 193
Novalung AV pump-less ECMO 620*f*
Novalung interventional lung assist 619
Nursing education, continuing (CNE) 106, 107
Nutrition 211, 325, 367
  enteral 522
  total parenteral 216, 248, 284, 522
Nutritional assessment in critically ill 521
Nutritional support 221, 260

O

Obese patient in ICU, care of 550
Obesity, classification of 550, 550*t*
Occult auto-positive end expiratory pressure 603
Occult positive end expiratory pressure 603
Older generation 621
Omega-3 fatty acids 524
Opioids 526, 538
Oral antibiotics, switchover to 188
Organ donors
  classification of 76
  management of 75, 77
Organ dysfunction 517*f*
  score, multiple 60*t*, 82, 82*t*
  syndrome
    mechanisms of multiple 57
      multiple (MODS) 57, 58*t*, 60t, 372
    organ failure, management of multiple 60
    pathogenesis of multiple 58*t*
    prevention of multiple 62
Organ failure
  assessment score 633*f*
  assessment, sequential (SOFA) 81, 82*t*
  index (OFI) 60
  multiple (MOF) 60
Organ grafts, poorly functioning 259
Organ system of hypokalemia 290*t*
Organisms causing pneumonia in inpatients 184*t*
Organochlorine 534
Organochlorine poisoning 537
Organophosphate poisoning 535
  treatment of 536
Organophosphates 526, 534
Organs, function of other 594
Orientia tsutsugamushi 463
Ornithine decarboxylase (ODC) 362
Oropharyngeal airway 11, 12*f*, 315
Oropharynx 9
Orthogonal polarization spectral (OPS) 35
Orthotopic liver transplantation 232, 233, 234*t*, 254
Oscillatory ventilation, high frequency 608, 614
Osmolar gap 279
Osmoreceptors 38
Otitis media, acute suppurative 449
Out-of-hospital cardiac arrest (OHCA) 65, 70
Oximes 536
Oxycodone 538
Oxygen 121, 410
  delivery, determinants of 24*fc*
  fraction of inspired 394, 538, 576, 610
Oxygenation 196, 599
  criteria 195
  extracorporeal membrane 125
  goal 610
Oxygenator 619

P

Paced ventricular complexes 143
Pacemaker 559
  on right side 559*f*
Pacing lead 156
Packed cell volume (PCV) 459
Pain management 247
Pain syndromes 374
Pain, severe 385
Palate, visualization of soft 20*f*
Pancreatic necrosis 222
Pancreatitis, acute 216
  severity in 217, 218*t*
Pancytopenia 526
Paralytic ileus 565*f*
Parameters, monitoring 390, 499
Parathion 534
Parathyroid hormone (PTH) 501
Parenteral nutrition 521, 522
  total (TPN) 434
Paroxysmal supraventricular tachycardia (PSVT) 134
  management of 135*fc*
Partial thromboplastin time (PTT) 517
  activated (APTT) 77
  with kaolin 544

by mansdocs.com

Passive leg raising 30, 41, 42, 391
Pathogen related 188
Pathogen-associated molecular patterns (PAMPs) 389
PDE-5 inhibitors 177
Peak airway pressure 569
Peak expiratory flow rate (PEFR) 365
Peak inspiratory pressure 569, 569*f*, 608, 611, 618
Pediatric assessment triangle (PAT) 381, 381*f*, 390
Pediatric intensive care units (PICU) 387
Pediatric lines 559
Pediatric septic shock 387, 390
PEEP, high versus low 199
PEEP, static and dynamic auto 570*f*
Percutaneous tracheostomy (PCT) 19
Percutaneous transhepatic biliary drainage 563
Peripheral parenteral nutrition 523
Peritoneal dialysis (PD) 430
Peritoneal lavage, diagnostic (DPL) 322
Peritonitis 430
Persistent precipitating pathology 509, 514
Personal digital assistant (PDA) 101
Phentolamine 150
Phlebostatic axis 26*f*
Placental gas exchange 360
Plasma Na+ and plasma osmolality, relationship between 301
Plasma osmolality 304
Plasma, disorders of 505
Plasmodium falciparum 465
Plateau pressures 367, 569
Platelet activating factor (PAF) 395
Platelets transfusion 395
Pleural effusion 562*f*
Pneumonia severity index (PSI) 186, 429
Pneumonia, classification of 184
Pneumonia, nonresponding 188
Pneumonia, severe 187
Pneumonic consolidation, subsegmental 563*f*
Pneumothorax on left side 556*f*
Pneumothorax, dressing of open 318*f*
Pneumothorax, management of open 318*f*
Poisoning, unknown 525
Poisons, symptoms caused by various 526*t*
Polycythemia 526
Polymerase chain reaction (PCR) 274, 434, 446, 458
Polymorphic ventricular tachycardia 139, 139*f*
Portal decompression wtih transjugular intrahepatic portosystemic shunt 232
Portal vein thrombosis (PVT) 254
Portocaval shunting (PCS) 245
Portopulmonary hypertension (PPH) 237, 255
Posaconazole 435, 440
Positive end expiratory pressure (PEEP) 17, 78, 174, 209, 247, 255, 367, 394, 414, 552, 570, 579, 581, 588, 593, 606, 611, 615
Positive predictive value (PPV) 434, 437
Positron emission tomography (PET) 414
Post-cardiac arrest
  brain injury 509
  bypass graft (CABG) 111
  myocardial dysfunction 509
  syndrome 508
    phases of 510*f*
Post-endoscopic retrograde cholangiopancreatography (ERCP) 216
Potassium abnormalities in diabetes ketoacidosis, management of 497*fc*
Potassium deficit 291
Potassium elimination, decreased 292
Potassium from body, elimination of 295
Potassium intake, decreased 289
Potassium preparations 291
Potassium, disorders of 289
Potassium, excessive loss of 290
Potassium, pathophysiology of 289
Pre-anhepatic phase 245
Predicted body weight (PBW) 198
Prediction rules 436
Predictive value, negative (NPV) 434, 437
Preeclampsia and eclampsia 151
Pre-emptive therapy 438
Pregnancy, physiology of 357
Pregnancy-induced hypertension (PIH) 151
Prehospital management 331
Premedication 241
Premedication drugs 606*t*
Pressure controlled ventilation (PCV) 579*f*, 581, 588, 603
Pressure cycled 573
Pressure regulated volume control (PRVC) 574
Pressure support (PS) 247, 334, 595
  mode 579
  ventilation 574, 578*f*, 593, 596
  with bi-level mode of ventilation 589
Pressure trigger 573, 576, 600*f*
Pressure ventilation 590
  non-invasive positive (NIV) 121
Pressure versus volume loop 571*f*
Pressure-support ventilation (PSV) 589
Pressure-targeted ventilation 577*f*
Pressure-time graphic waveform 580*f*
Pressure-time waveform 580
Pressure-volume (PV) 581, 587
Pressurized metered dose inhalers (PMDIs) 621
Prone positioning 614
Prone ventilation 367, 613
Prophylaxis for stress ulceration 208
Prophylaxis, infection 247, 274
Propofol 403
Prostacyclins 176
Prothrombin time (PT) 77, 243, 456, 517
  active (APTT) 324
  index (PTI) 544
Proton pump inhibitors (PPIS) 395
Proximal airway, secretions in 192
Proximal renal tubular acidosis 283
Pseudohyperkalemia 292
Pseudomonas aeruginosa 428
PTH and serum calcium 307
Pulmonary angiogram 365
Pulmonary angiography 231
Pulmonary ARDS 196
Pulmonary arterial wedge pressure (PAWP) 517
Pulmonary artery
  catheter (PAC) 29, 29*f*, 172, 199, 241, 557
  diastolic pressure (PADP) 627
  occlusion pressure (PAOP) 24, 41, 195, 628
  pressure 174, 627
  studies 547
  systolic pressure 627
  wedge pressure (PAWP) 627
Pulmonary aspergillosis, invasive 429
Pulmonary capillary wedge pressure (PCWP) 54
Pulmonary contusion 608
Pulmonary disease, chronic obstructive (COPD) 135, 161, 231, 427, 435, 506, 595, 603, 621
Pulmonary drug delivery system for
  extubated patients 625*f*
  ventilated patients 624*f*
Pulmonary drug delivery systems 624
Pulmonary edema, acute cardiogenic 597
Pulmonary embolism (PE) 160, 161*t*, 163, 166, 553
  massive 162
  probability of 162
  severity index (PESI) 163
  submassive 163

by mansdocs.com

Pulmonary embolus (PE) 518
Pulmonary function testing (PFT) 231, 552*t*
Pulmonary hypertension 367
Pulmonary infections 451
Pulmonary system 254
Pulmonary vascular resistance (PVR) 172, 627
  index (PVRI) 627
Pulmonary vasodilators 176
Pulse contour analysis computer (PICCO) 256
Pulse generator 155
Pulse pressure variation (PPV) 30, 41, 43, 43*f*, 391
Pulseless electrical activity (PEA) 71
PV loops, abnormal 583
Pyridoxine infusion 403

Q

QRS complex failure to capture 158*f*
QRS complex tachycardia, supraventricular narrow 130*fc*
Quinine 459

R

Randomized controlled trials (RCTs) 222, 553, 613
Ranson criteria 217
Rapid infusion system 245*f*
Rapid sequence intubation (RSI) 18, 316, 382, 400, 606
Rapid shallow breathing index (RSBI) 594
Rebleeding 340
  to anterior communicating artery 341*f*
Recruitable lung, identify 611
Recruitment maneuver (RM) 611, 612
  prolonged 611
  types of 611
Red blood cells (RBC) 60, 457, 535
Red cells, disorders of 505
Regional wall motion abnormality (RWMA) 120
Rehabilitation 327
Reintubation 592
Renal biopsy 266
  in acute kidney injury 265*t*
Renal disease
  diet in 553
  end-stage 430
Renal equations 631
Renal failure
  acidosis to 281
  acute 226, 267, 268, 499, 631
  chronic 277
  management 211
  pathophysiology of acute 499
Renal formulae and values 631
Renal function 325
  assessment of 263
Renal of potassium loss 290
Renal preglomerular vasoconstriction in hepatorenal syndrome 239
Renal replacement therapy (RRT) 93, 229, 257, 267
  advantages of 272
  continuous 279
  disadvantages of continuous 272
  principles of 269
Renal system 238, 257, 513
Renal transplant recipients, management of 273
Renal tubular acidosis (RTA) 290
  disorders with 283*t*
Renin-angiotensin-aldosterone system (RAAS) 118
Rescue strategies in ARDS 610
Rescue strategy in acute respiratory distress syndrome 610
Rescue therapy in ARDS 613
Residual capacity, functional (FRC) 334, 358, 374, 552*t*, 572, 602
Respiratory 332
  acidosis 284
  alkalosis 284
  complications 333
  compromise 608
  control 323
  depression 539
  disorders during pregnancy 364
  distress syndrome, acute (ARDS) 54, 170, 195, 196*f*, 254, 364, 365, 388, 449, 456, 459, 518, 588, 610, 613, 618, 621
    causes of (ARDS) 366*t*
  dysfunction 332
  failure 373, 385
    acute 573, 587
    management of 413
    treatment of acute 592
  failure, types of 5, 6*fc*
  load 593
  management 332
  mechanics: basics 569
  monitoring 349
  rate (RR) 597
  support 162
  system 513
Resting energy expenditure (REE) 553
Restrictive cardiomyopathy (RCM) 118
Resuscitation of septic shock 394
Resuscitation regimens 488
Resuscitation syndrome, phases of 509
Resuscitation, initial 162
Rheumatic arthritis (RA) 449
Rheumatologic syndromes 449
RV afterload, decrease 176
RV perfusion pressure 174

S

SAH complications, management of 339
SAH, non-neurological complications of 343
Salicylate intoxication 281
Saline correction 303
Saline solution (NS) 40
Saline, normal 256
Salivation 535
Salt infusions 303
Salvage therapy 439
Scalds injury 485
Sclerosing cholangitis, primary 370
Score allocation in PSI, step 2 186*t*
Scorpion envenoming treatment 548*t*
Scorpion sting 546
Scrub typhus 463, 467
Sedation and weaning 191
Sedimentation 621
Seizure 349
  control 343
  prevention of 414
  termination of 401
Selenium 524
Semipermeable membrane 269*f*
Sengstaken-Blakemore tube 559
Sensitivity, testing 156
Sepsis 34
  and related terminology 389
  severity of 389
Septic shock 34, 54, 387, 388, 392, 396
  early recognition of 390
Serum albumin and serum calcium, relation of 306
Serum antibodies 185
Serum calcium 306
  regulation of 306
Serum creatinine phosphokinase 527
Serum lactate dehydrogenase (LDH) 217
Serum lactates 31
Serum markers 175*t*
Serum viscosity (SV) 505
Servo ultra nebulizer 345 series 623*f*
Severity of cirrhosis, classification of 227*t*
Severity, assessment of 217
Shock
  causes of 6, 319
  severity of 319
  signs of 319
  symptoms of 319

by mansdocs.com

Sildenafil 177
Sinus arrest 141
Sinus bradycardia 141
Sinus node
  abnormalities 141
  dysfunction 155
  exit block 141*f*
Sinus rhythm 129, 130*f*
Sinus tachycardia 130, 131*f*
Skeletal 335
Skin and soft tissue infections 427, 431
Skin, color of 319
Smoke inhalation 486
Snake envenomation 543
  signs of 544*t*
  symptoms of 544*t*
Snake venom components and effects 543*t*
Snakebite 543
Sodium correction 304
Sodium disorders 296
Sodium nitroprusside (SNP) 147, 149
Sodium, fractional excretion of 304
Solute removal 270*f*
Space-occupying lesions (SOLs) 373
Spider bite 547
Spinal cord compression 504
Spinal injury, management of 329
Spontaneous circulation, return of 67, 70, 508
Spontaneous recovery 212
Sputum gram stain and culture 185
Staphylococcus 211
  aureus 428
Stasis, zone of 484
Statin therapy 115
Status epilepticus 398, 399*t*, 401*t*
  treatment of 400
Sterile necrosis 222
Stippling 526
Streptococcus 211
  pneumoniae 183, 187, 428
Stress disorder, post-traumatic (PTSD) 477
Stress-related bleeding, prevention of 191
Stroke index (SI) 628
Stroke volume (SV) 23, 42, 627
  index (SVI) 627
  variation 30, 41, 43, 44*f*
ST-segment
  analysis (STAN) 374
  elevation myocardial infarction 114
Subarachnoid aneurysm trial 340
Subarachnoid haemorrhage
  causes of 337*t*
  diffuse 339
  management of 337
Subglottic aspiration 191
Sublingual capnometry 35
Sudden cardiac deaths (SCDs) 64
Sulphydryl variable (SHV) 421
Superior vena cava (SVC) 391, 498, 518
  syndrome 503
Supportive therapy 536
Supraventricular tachycardia, management of 132
Sustained inflation 611
  maneuver 611
SVC syndrome, causes of 503
Swan-Ganz catheter 557
Sweep gas 618
Sympathetic crisis 151
Sympathetic nervous system 228
Sympathomimetics 526
Symptomatic hyponatremia, management of 303
Symptomatic patient 304
Synchronized intermittent mandatory ventilation (SIMV) 574, 579
Systemic complications after neurosurgery
  management of 347
  prevention of 347
Systemic inflammatory response syndrome (SIRS) 57, 217, 388, 518, 524
Systemic lupus erythematosus (SLE) 372, 449
Systemic management 254
Systemic secondary insults 348*t*
Systemic vascular resistance (SVR) 29, 387, 517, 547, 627
Systolic blood pressure (SBP) 77, 383*t*, 390, 594, 627
Systolic pressure variation (SPV) 30

T

Tachyarrhythmias
  mechanisms of 129
  supraventricular 129
Tachycardia 155
  multifocal atrial 135, 136*f*
  supraventricular 138
Tadalafil 177
Taphylococcus aureus 183
Tazobactam 424
TBI, intubation in 605, 606
Temperature monitoring 73, 244, 351
Temperature regulation 394
Tension pneumocephalus 349
Tension pneumothorax, management of 318*f*
Tertiary termination criteria 599
Therapeutic hypothermia 70, 73, 511
Therapeutic hypothermia, phases of 513*f*
Thermal injuries 485
Thermoregulation 378
Third degree AV block 143
Thoracocentesis 192
Thoracotomy 192
Threshold, testing 156
Thrombocytopenia 526
Thromboelastography 235, 243, 258
Thromboelastometry, rotation 243
Thrombolysis in myocardial infarction (TIMI) 114
Thrombolytic therapy 167*t*
  protocol 165
Thromboplastin time, activated partial (APTT) 243
Thrombosis prophylaxis 348
Tidal volume 367, 588, 607
  higher 174
Tigecycline 424
Tiny echogenic specks representing air bubbles 562*f*
Tissue hypoxia-microvascular hypothesis 59
Tissue plasminogen activator (TPA) 553
Tongue obstructing airway 10*f*
Toxidromes, identification of 525
Toxin ingestion, acidosis to 281
Tracheobronchial injury 608
Tracheostomy 19, 333
  tube 556
Transcellular potassium shifts 289
Transcranial Doppler 351
  ultrasonography 339
Transcutaneous cardiac pacing 154
Transesophageal echocardiography (TEE) 44, 132, 147, 164, 231, 242
Transfusion protocol, massive (MTP) 320
Transfusion triggers 619
Transjugular intrahepatic portosystemic shunt (TIPS) 226, 229, 229*f*, 238, 431
Transplant patient, evaluation of 233*f*
Transthoracic echocardiography 44
Transversus abdominis plane (TAP) 374
Trauma 216
  care, generic approach to 314
  life support, advanced (ATLS) 313, 330
  patient, management of critically ill 313
Traumatic brain injury (TBI) 71, 313, 337, 347, 407, 408, 605
Treating underlying causes 299
Triad, diagnostic 191
Triage 314
Tricyclic antidepressants 526

by mansdocs.com

Trigger variable 573
Triggering 599
Troponin 113
Trypsinogen-activated peptide (TAP) 217
T-tube or pressure support 595
Tube compensation, automatic 589
Tubular necrosis, acute 257, 518
Tumor lysis syndrome 498, 499
  pathophysiology of 499
  treatment of 500
Tumor necrosis factor (TNF) 457
Tumorlysis syndrome 499
  conditions with 498, 498*t*
Two-event hypothesis 59
Two-stage approach to weaning 595

U

Ultrafiltration 269
Umbilical vein 361
Unfractionated heparin 164, 164*t*
Univariate analysis 83
Univent tube with bronchial blocker 607*f*
Upper inflection point (UIP) 582
Urinary acidification 529
Urinary alkalinization 529
Urinary catheter 321
Urinary Na+ concentration 304
Urinary output 319
Urinary tract 452
  infection (UTI) 427, 449
Urine 527
  antigen tests 185
  in different conditions 631
  osmolality 304
  output, low 25
  urea nitrogen (UUN) 521
Uterine artery 361
Uterine blood flow 360
Uterine vein 361
Uvula, visualization of 20*f*

V

Vagal syncope 399
Varicella-zoster virus (VZV) 216
Vascular beds in cirrhosis, circulatory changes in different 237*t*
Vascular endothelial growth factor (VEGF) 237
Vascular resistance, low systemic 228
Vascular thrombosis 260
Vasoactive peptide (VIP) 230
Vasopressin antagonist 123
Vasopressor/ionotropic support 162
Vaughan-Williams classification 139*t*
Vein, thrombosis of 565*f*
Vena cava, superior 556
Venous access, advanced (AVA) 244
Venous oximetry 32
  limitations of 34
  mixed 391
Venous thromboembolism (VTE) 160, 324, 335, 553
Venovenous bypass (VVB) 244
Venovenous extracorporeal membrane oxygenation 618*f*
Venovenous hemodiafiltration
  continuous 271
  principle of continuous 271*f*
Venovenous hemodialysis, continuous 271
Venovenous hemofiltration
  continuous 270, 271*f*
  principle of continuous 271*f*
Ventilation
  basic modes of 576
  controlled 614
  effects of mechanical 173
  emerging modes of non-invasive 601
  failure, non-invasive 600
  in ARDS lungs, positive pressure 197
  in asthma 603
  in prone position 613*f*
  in TBI 606
  in weaning, role of non-invasive 595
  inverse ratio 367
  mechanical 43, 434, 437, 552
  newer modes of 587
  non-invasive 6, 334, 552, 590, 595, 596, 603, 626
    positive pressure (NIPPV) 590
  perfusion 230
  positive pressure 573
  pressure-targeted 578*f*
  principles of mechanical 573
  procedures in ARDS net study 198*t*
  proportional assist (PAV) 574, 590, 601
  spontaneous 43
  strategy in obstructive airway disease 602
  strategy in trauma 605
  synchronized intermittent mandatory 578
  targets of 573
  volume controlled 577*f*, 581, 588
  volume-targeted 579*f*
  waveforms in modes of 581
  weaning from mechanical 334
  weaning/liberation from mechanical 592
Ventilator graphics 580
Ventilator in spontaneously breathing patients 574
Ventilator loops 581
Ventilator procedures 199
Ventilator waveforms 580
Ventilator, non-invasive 247
Ventilator, rest settings on 619
Ventilator-associated
  pneumonia (VAP) 190, 429, 592, 614
  tracheobronchitis (VAT) 193
Ventilator-induced lung injury (VILI) 611, 613
Ventilators providing NIV, performance for 598
Ventilators to provide NIV 598
Ventilatory assist, neurally adjusted 574, 590
Ventilatory breath cycle, components of 576*t*
Ventilatory flow patterns 581*f*
Ventilatory setting 618
Ventilatory strategies in ARDS 197
Ventilatory support, postoperative 246
Ventricle, left 147, 162, 169, 343, 628
Ventricle, right (RV) 158, 169, 588
Ventricular apex, right 158*f*
Ventricular assist devices 126, 396
Ventricular diastolic pressure, right (RVDP) 627
Ventricular ejection fraction
  left (LVEF) 115
  right (RVEF) 172, 628
Ventricular end-diastolic volume, left (LVEDV) 118
Ventricular end-diastolic volume, right (RVEDV) 628
Ventricular end-systolic volume
  left (LVESV) 118
  right (RVESV) 628
Ventricular failure
  cause of acute right 170*t*
  diagnosis of acute right 175*t*
  right (RVF) 169, 170, 171*f*, 196
  treatment of right 173
Ventricular fibrillation (VF) 68*f*, 70, 127, 140, 140*f*, 154
Ventricular function, right 171, 173
Ventricular hypertrophy, left (LVH) 112
Ventricular performance, right 174
Ventricular premature complex 136, 136*f*
Ventricular pressure, right (RVP) 627
Ventricular stroke work
  index, right (RVSWI) 627
  left (LVSW) 627
  right (RVSW) 627
Ventricular systolic pressure, right (RVSP) 627
Ventricular tachyarrhythmias 136
Ventricular tachycardia 68*f*, 70, 127, 136, 137
  monomorphic 137*f*

by mansdocs.com

Viral hepatitis 206, 370
in pregnancy, acute 370*t*
Viral infections 204
Viral pneumonias, treatment of 188
Vital capacity, forced 332, 350
Vitamin D dependent rickets 307
Vitamin D-linked hypercalcemia 501
Vitamin K 208
Vitamin mediated 307
Vitamins and trace elements 523
Volume-control mode 578
Volume-controlled ventilation vs pressure-controlled ventilation 582*f*
Volume-targeted ventilation 577*f*
Volume-time and flow-time waveforms 583*f*
Voriconazole 435, 440

W

Waldenstrom macroglobulinemia (WM) 505
Wallace rule of nines 487
Warm shock 387
Warning scoring system, early 3*t*
Water homeostasis 296, 297*f*, 301*f*
Weaning failure 593
Weaning from ECMO 619
Weaning outcome 593*t*
Weaning, difficult 593
Weaning, prolonged 593
Weaning, simple 593
Weil's disease 468
Well's score 163*t*
Wenckebach's phenomenon 142
White blood cell (WBC) 57, 505
WHO of severe dengue fever 460*t*
Whole blood clotting test (WBCT) 544
Whole-brain radiation therapy (WBRT) 504
Wide complex tachycardia 138*fc*
Worsening airflow obstruction 602
Wound infection, preventing invasive 491

by mansdocs.com